Derek S. Wheeler
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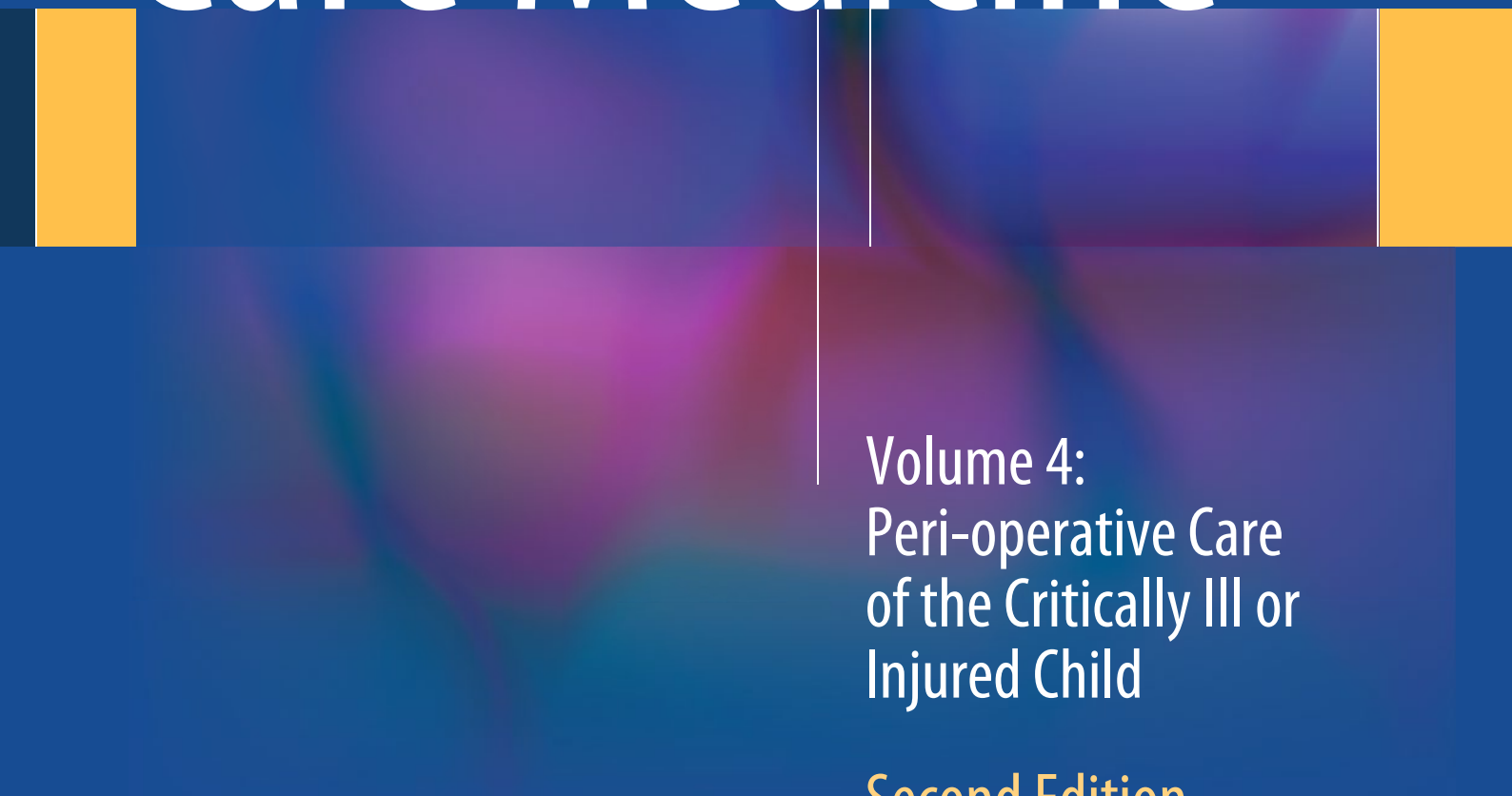
Editors

Pediatric Critical Care Medicine



Volume 4: Peri-operative Care of the Critically Ill or Injured Child

Second Edition

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For Cathy, Ryan, Katie, Maggie, and Molly

"You don't choose your family. They are God's gift to you…"
Desmond Tutu

Foreword to the First Edition

The practitioner of *Pediatric Critical Care Medicine* should be facile with a broad scope of knowledge from human developmental biology, to pathophysiologic dysfunction of virtually every organ system, and to complex organizational management. The practitioner should select, synthesize and apply the information in a discriminative manner. And finally and most importantly, the practitioner should constantly "listen" to the patient and the responses to interventions in order to understand the basis for the disturbances that create life-threatening or severely debilitating conditions.

Whether learning the specialty as a trainee or growing as a practitioner, the pediatric intensivist must adopt the mantle of a perpetual student. Every professional colleague, specialist and generalist alike, provides new knowledge or fresh insight on familiar subjects. Every patient presents a new combination of challenges and a new volley of important questions to the receptive and inquiring mind.

A textbook of pediatric critical care fills special niches for the discipline and the student of the discipline. As an historical document, this compilation records the progress of the specialty. Future versions will undoubtedly show advances in the basic biology that are most important to bedside care. However, the prevalence and manifestation of disease invariably will shift, driven by epidemiologic forces, and genetic factors, improvements in care and, hopefully, by successful prevention of disease. Whether the specialty will remain as broadly comprehensive as is currently practiced is not clear, or whether sub-specialties such as cardiac- and neurointensive care will warrant separate study and practice remains to be determined.

As a repository of and reference for current knowledge, textbooks face increasing and imposing limitations compared with the dynamic and virtually limitless information gateway available through the internet. Nonetheless, a central standard serves as a defining anchor from which students and their teachers can begin with a common understanding and vocabulary and thereby support their mutual professional advancement. Moreover, it permits perspective, punctuation and guidance to be superimposed by a thoughtful expert who is familiar with the expanding mass of medical information.

Pediatric intensivists owe Drs. Wheeler, Wong, and Shanley a great debt for their work in authoring and editing this volume. Their effort was enormously ambitious, but matched to the discipline itself in depth, breadth, and vigor. The scientific basis of critical care is integrally woven with the details of bedside management throughout the work, providing both a satisfying rationale for current practice, as well as a clearer picture of where we can improve. The coverage of specialized areas such as intensive care of trauma victims and patients following congenital heart surgery make this a uniquely comprehensive text. The editors have assembled an outstanding collection of expert authors for this work. The large number of international contributors is striking, but speaks to the rapid growth of this specialty throughout the world.

We hope that this volume will achieve a wide readership, thereby enhancing the exchange of current scientific and managerial knowledge for the care of critically ill children, and stimulating the student to seek answers to fill our obvious gaps in understanding.

Chicago, IL, USA — Thomas P. Green
New Haven, CT, USA — George Lister

Preface to the Second Edition

The specialty of pediatric critical care medicine continues to grow and evolve! The modern PICU of today is vastly different, even compared to as recently as 5 years ago. Technological innovations in the way we approach the diagnosis and treatment of critically ill children have seemingly changed overnight in some cases. Vast improvements in anesthesia and surgical techniques have resulted in better outcomes and shorter lengths of stay in the PICU. The outcomes of conditions that were, even less than a decade ago, almost uniformly fatal have greatly improved. Advances in molecular biology have led to the era of personalized medicine – we can now individualize our treatment approach to the unique and specific needs of a patient. We now routinely rely on a vast array of condition-specific biomarkers to initiate and titrate therapy. Some of these advances in molecular biology have uncovered new diseases and conditions altogether! At the same time, pediatric critical care medicine has become more global. We are sharing our knowledge with the world community. Through our collective efforts, we are advancing the care of our patients. Pediatric critical care medicine will continue to grow and evolve – more technological advancements and scientific achievements will surely come in the future. We will become even more global in scope. However, the human element of what pediatric critical care providers do will never change. "For all of the science inherent in the specialty of pediatric critical care medicine, there is still art in providing comfort and solace to our patients and their families. No technology will ever replace the compassion in the touch of a hand or the soothing words of a calm and gentle voice" [1]. I remain humbled by the gifts that I have received in my life. And I still remember the promise I made to myself so many years ago – the promise that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for these gifts. It is my sincere hope that the second edition of this textbook will educate a whole new generation of critical care professionals, and in so-doing help me continue my promise.

Cincinnati, OH, USA — Derek S. Wheeler, MD, MMM

Reference

1. Wheeler DS. Care of the critically ill pediatric patient. Pediatr Clin North Am 2013;60:xv–xvi. Copied with permission by Elsevier, Inc.

Preface to the First Edition

Promises to Keep

The field of critical care medicine is growing at a tremendous pace, and tremendous advances in the understanding of critical illness have been realized in the last decade. My family has directly benefited from some of the technological and scientific advances made in the care of critically ill children. My son Ryan was born during my third year of medical school. By some peculiar happenstance, I was nearing completion of a 4-week rotation in the Newborn Intensive Care Unit. The head of the Pediatrics clerkship was kind enough to let me have a few days off around the time of the delivery – my wife Cathy was 2 weeks past her due date and had been scheduled for elective induction. Ryan was delivered through thick meconium-stained amniotic fluid and developed breathing difficulty shortly after delivery. His breathing worsened over the next few hours, so he was placed on the ventilator. I will never forget the feelings of utter helplessness my wife and I felt as the NICU Transport Team wheeled Ryan away in the transport isolette. The transport physician, one of my supervising third year pediatrics residents during my rotation the past month, told me that Ryan was more than likely going to require ECMO. I knew enough about ECMO at that time to know that I should be scared! The next 4 days were some of the most difficult moments I have ever experienced as a parent, watching the blood being pumped out of my tiny son's body through the membrane oxygen-

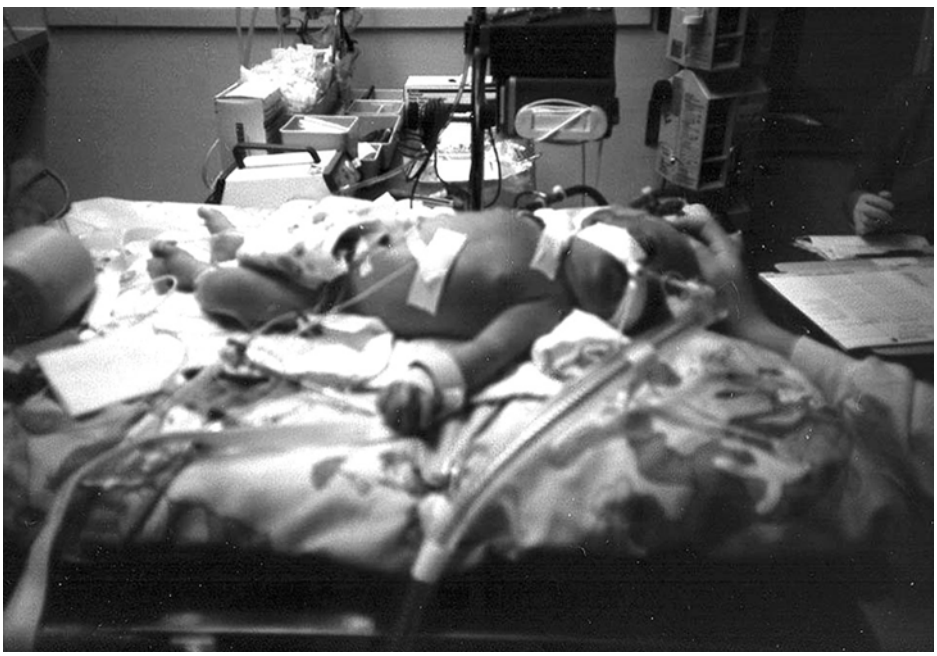

Fig. 1

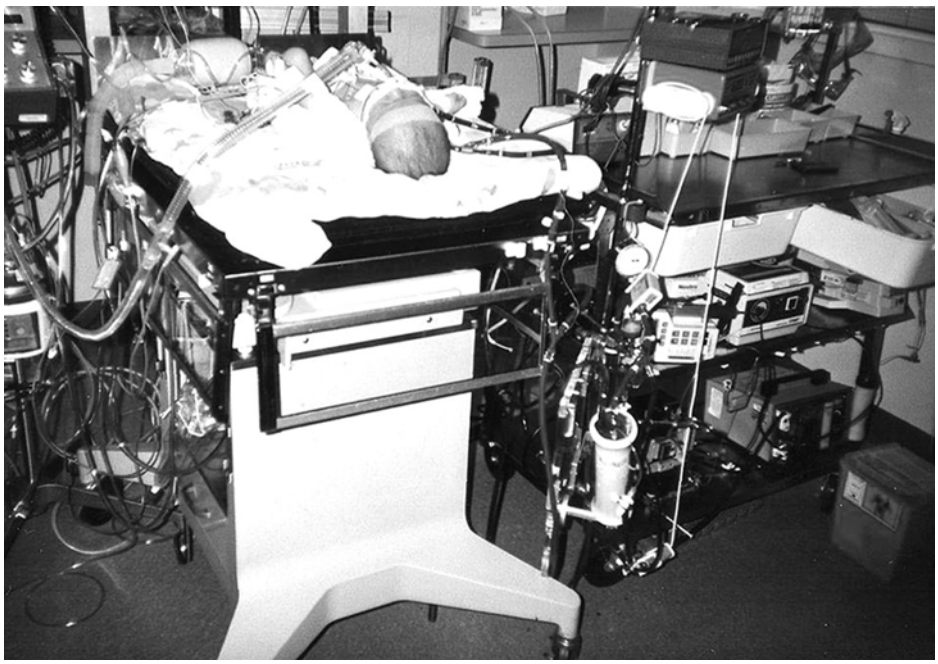

Fig. 2

ator and roller pump, slowly back into his body (Figs. 1 and 2). I remember the fear of each day when we would be told of the results of his daily head ultrasound, looking for evidence of intracranial hemorrhage, and then the relief when we were told that there was no bleeding. I remember the hope and excitement on the day Ryan came off ECMO, as well as the concern when he had to be sent home on supplemental oxygen. Today, Ryan is happy, healthy, and strong. We are thankful to all the doctors, nurses, respiratory therapists, and ECMO specialists who cared for Ryan and made him well. We still keep in touch with many of them. Without the technological advances and medical breakthroughs made in the fields of neonatal intensive care and pediatric critical care medicine, things very well could have been much different. I made a promise to myself long ago that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for the gifts that we, my wife and I, have been truly blessed. It is my sincere hope that this textbook, which has truly been a labor of joy, will educate a whole new generation of critical care professionals, and in so-doing help make that first step towards keeping my promise.

Acknowledgements

With any such undertaking, there are people along the way who, save for their dedication, inspiration, and assistance, a project such as this would never be completed. I am personally indebted to Michael D. Sova, our Developmental Editor, who has been a true blessing. He has kept this project going the entire way and has been an incredible help to me personally throughout the completion of this textbook. There were days when I thought that we would never finish – and he was always there to lift my spirits and keep me focused on the task at hand. I will be forever grateful to him. I am also grateful for the continued assistance of Grant Weston at Springer. Grant has been with me since the very beginning of the first edition of this textbook. He has been a tremendous advocate for our specialty, as well as a great mentor and friend. I would be remiss if I did not thank Brenda Robb for her clerical and administrative assistance during the completion of this project. Juggling my schedule and keeping me on time during this whole process was not easy! I have been extremely fortunate throughout my career to have had incredible mentors, including Jim Lemons, Brad Poss, Hector Wong, and Tom Shanley. All four are gifted and dedicated clinicians and remain passionate advocates for critically ill children, the specialties of neonatology and pediatric critical care medicine, and me! I want to personally thank both Hector and Tom for serving again as Associate Editors for the second edition of this textbook. Their guidance and advice has been immeasurable. I have been truly fortunate to work with an outstanding group of contributors. All of them are my colleagues and many have been my friends for several years. It goes without saying that writing textbook chapters is a difficult and arduous task that often comes without a lot of benefits. Their expertise and dedication to our specialty and to the care of critically ill children have made this project possible. The textbook you now hold in your hands is truly their gift to the future of our specialty. I would also like to acknowledge the spouses and families of our contributors – participating in a project such as this takes a lot of time and energy (most of which occurs outside of the hospital!). Last, but certainly not least, I would like to especially thank my family – my wife Cathy, who has been my best friend and companion, number one advocate, and sounding board for the last 22 years, as well as my four children – Ryan, Katie, Maggie, and Molly, to whom I dedicate this textbook and all that I do.

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Part I

Anesthesia in the Critically Ill or Injured Child

Stephen D. Playfor

Preparing the Critically Ill or Injured Child for Surgery

1

Nancy S. Hagerman and Anna M. Varughese

Abstract

The identification and assessment of perioperative risk factors in the critically ill child requiring surgery is important, because targeting these risk factors allows the creation of care plans that can significantly improve outcomes. This chapter provides an overview of the preoperative assessment and preparation of these patients for surgery. It reviews fasting guidelines, provides a systems-approach to the preoperative assessment, administration of preoperative medications, and determination of which preoperative laboratory or radiological data to attain. Appropriate access and monitoring, risk involved in the transportation process, reducing surgical site infections in the pediatric patient, and the importance of effective multidisciplinary communication and communication with patients and their families is also addressed.

Keywords

Preoperative assessment • ICU • Critical care • Pediatric anesthesia • Preoperative evaluation

Introduction

Although the incidence of intraoperative death associated with anesthesia has declined dramatically over the past several decades, perioperative morbidity and mortality in critically ill patients continues to be high, particularly in those patients who exhibit known risk factors. An individual patient's perioperative risk includes both surgical as well as anesthetic risks associated with their underlying disease state. Established risk factors in the pediatric population include a higher ASA physical status (a classification system used to describe a patient's physical state ranging from 1 to 6) (Table 1.1), age (especially those patients under 1 year), emergency surgery, existence of an underlying disease and type of disease, and location of the intervention (operating room vs. non-operating room) [1]. Due to the continual evolution of the practice of medicine, a comprehensive and accurate assessment of a patient's perioperative risk can be difficult. However, it is important to target those factors that can be identified for intervention, because in so doing, the associated risk can be decreased [2]. This chapter will focus on those factors for which intervention can be performed to optimize outcomes in the critically ill child preparing for surgery.

Fasting Guidelines

In 2011, the American Society of Anesthesiologists updated their guidelines for preoperative fasting to reduce the risk of pulmonary aspiration in patients presenting for surgery [3].

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Table 1.1 ASA physical status classification system

ASA 1	A normal, healthy patient
ASA 2	A patient with mild systemic disease
ASA 3	A patient with severe systemic disease
ASA 4	A patient with severe systemic disease that is a constant threat to life
ASA 5	A moribund patient who is not expected to survive without the operation
ASA 6	A declared brain-dead patient whose organs are being removed for donor purposes

For elective surgery, the guidelines include a fasting interval of two of more hours after the consumption of clear liquids, four or more hours after breast milk in both neonates and infants, six or more hours after the intake of infant formula, and six or more hours after a light meal or non-human milk. These guidelines, however, are intended only for healthy patients undergoing elective procedures. The guidelines do not extend to critically ill patients with co-existing diseases or conditions that may affect gastric emptying or gastric fluid volume such as pregnancy, obesity, diabetes mellitus, hiatal hernia, gastroesophageal reflux disease, or bowel obstruction. Additionally, the guidelines are not considered appropriate for patients in whom difficult airway management may be anticipated [3]. The determination of what constitutes a safe preoperative fasting duration is difficult as the incidence of pulmonary aspiration is very low, estimated between 1 in 10,000 and 10 in 10,000 [4]. In a large prospective study, Warner et al. found that there was a greater frequency of aspiration in emergency procedures versus elective procedures, and that the majority of infants and children less than 3 years of age who aspirated had associated ileus or bowel obstruction [5]. They also found that most children who have mild or moderate aspiration events have no significant medical sequelae. The ASA guidelines do not provide any recommendations regarding patients who are fed enterally. It is the practice of the authors to apply the above guidelines for clear liquids and or formula to gastric tube feeds. Jejunal feeds, however, are beyond the pylorus and should thus provide a level of protection against the risk of pulmonary aspiration. Thus, one could reasonably argue that the guidelines do not apply to this patient population.

The impact of medications and their interactions on a patient's medical and/or surgical risk should also be considered when determining which medications should be given or held during the preoperative period. For example, antiplatelet agents and anticoagulants are likely to be contraindicated in the perioperative setting unless the benefits of continuing these medications outweigh the risk of increased surgical blood loss. However, a patient's chronic medications should be continued and can include antiarrhythmic, antihypertensive, asthma, diabetes, immunosuppressive, antiseizure, and psychiatric medications. Specific considerations as to which drugs to continue perioperatively are dependent upon surgical, patient, and pharmacologic factors [6].

The preoperative history should also include an understanding of the patient's home medication regimen, particularly if the patient had been hospitalized in the recent past. It has been estimated that approximately 16 % of the pediatric population receives or has received herbal medications [7]. It is also concerning that a large proportion of the patient population does not disclose the use of these remedies to their healthcare provider. Many herbal supplements have the potential to react adversely with anesthetic agents. Some are known to have effects on platelet aggregation and/or the clotting cascade, while others may cause immunosuppression or potentiate central nervous system depression perioperatively. Other herbal supplements can significantly affect hemodynamics intraoperatively [7]. For example, gingko biloba, garlic, ginger, fish oil, and flax seed oil decrease platelet aggregation, chamomile inhibits clotting, vitamin E affects coagulation, and prolonged use of echinacea can cause immunosuppression increasing a patient's risk of wound infection [7, 8]. In the critically ill child requiring urgent or emergent surgery, knowledge of the use of herbal supplements should be communicated with the operative team to add to the understanding of a patient's pathophysiology in the event an adverse outcome were to occur intraoperatively.

Systems-Based Approach to Preoperative Assessment

Careful preoperative assessment is necessary to tailor patient management to their specific needs. A systems-based approach to the preoperative assessment is a useful way to assess and prepare the patient for surgery.

Respiratory

The majority of adverse events that transpire intraoperatively in the pediatric population occur secondary to a respiratory etiology [1]. Age is an independent risk factor for respiratory events. This is thought to be due to the highly compliant chest wall of the infant which can lead to an increased tendency of airway collapse. Infants also exhibit a high vagal tone that can lead to apnea or laryngospasm following vagal stimulation due to increased secretions, tracheal intubation, or airway suctioning [1]. Other known risk factors for respiratory events include a history of bronchopulmonary dysplasia (BPD), asthma, bronchial reactivity, recent upper respiratory tract infection, exposure to passive smoking, and history of prematurity.

Bronchopulmonary dysplasia places children at risk for exaggerated pulmonary vasoconstriction and subsequent

V/Q mismatch which can lead to profound hypoxemia, particularly during the first year of life. Stimuli specific to the perioperative period, namely hypothermia, pain, and acidosis, can trigger pulmonary vasoconstriction and thus increase V/Q abnormalities in a child who already has a limited reserve [9]. Severe BPD can also lead to right ventricular function impairment that can be worsened by anesthesia. If cardiac dysfunction is suspected, an echocardiogram should be performed preoperatively [1]. Measures that can be taken to optimize children with BPD preoperatively include the use of corticosteroids, bronchodilators, antibiotics, and diuretics, as indicated [9].

Asthma also places children at risk perioperatively. Bronchial hyperreactivity can persist for several weeks following an acute asthmatic episode, often for several weeks after the inciting event when clinical symptoms are no longer present [1]. Commonly performed procedures in the ICU as well as during anesthesia can serve as intense stimuli that can provoke bronchospasm. These procedures include laryngoscopy, intubation, and suctioning of the airway [1]. Intraoperative bronchospasm can be disastrous as it can make ventilation difficult, if not impossible resulting in hypercarbia, acidosis, hypoxia, cardiovascular collapse, and even death [9]. These patients should be maximally optimized prior to entering the operating room when possible. In general, asthma medical therapy should be escalated prior to surgery even in well-controlled asthmatics. Increased use of inhalers, nebulizers, and steroids (inhaled and oral) has been advocated in this patient population [9]. A "steroid burst" of methylprednisolone 1 mg/kg [1] or prednisone 1 mg/kg/day [9] for 3–5 days should be administered for the child with severe reactive airways or asthma prior to their procedure.

Children who were intubated and ventilated as neonates are at increased risk for subglottic stenosis [9]. A history of croup or stridor can sometimes herald a diagnosis of subglottic stenosis. When preparing for intubation in these patients, one should have endotracheal tubes 0.5–1 mm smaller internal diameter available. Infants with a history of prematurity (<37 weeks gestation) are also at increased risk of postoperative apnea (>15 s) and periodic breathing for up to 24 h postoperatively [9]. Although all individuals experience respiratory depression in response to sedation and anesthesia, former premature infants are at increased risk given the immaturity of their peripheral and central chemoreceptors and their response to hypoxia and hypercarbia [9]. Former premature infants with anemia (hematocrit < 30) are at particular risk of postoperative apnea. This risk can be decreased by delaying surgery, if possible until 48–60 weeks postgestational age. If surgery must be performed, the perioperative administration of caffeine (10 mg/kg caffeine base IV or 20 mg/kg caffeine citrate or benzoate) has been shown to be effective in dramatically reducing post-operative apnea in this patient population.

Cardiovascular

When preparing a child for surgery, cardiovascular considerations include the presence of a murmur, congenital heart disease, pulmonary hypertension, the potential need for SBE prophylaxis, and awareness of conduction abnormalities. Although innocent murmurs are common in the pediatric population, it is important to be aware of any structural abnormalities prior to entering the operating room. If there is any concern regarding a murmur such as a co-existing history of cyanotic episodes, poor exercise tolerance, or failure to thrive – an echocardiogram and evaluation by a pediatric cardiologist should be obtained prior to surgery. Given that most anesthetics and sedatives cause cardiac depression, knowledge of a patient's baseline cardiac function prior to entering the operating room is invaluable.

Most anesthetic agents decrease vascular tone and subsequently decrease systemic and pulmonary vascular resistance [9]. This can, in turn, significantly affect the hemodynamic equilibrium in a patient with an intra-cardiac shunt. For example, a patient with a ventricular septal defect (left-to-right shunt) could experience pulmonary overcirculation and failure. Alternatively, in the setting of hypoxia, hypercarbia, or acidosis, this same patient could experience this shunt shifting to a right-to-left shunt due to an increase in pulmonary vascular resistance [9]. Patients with intra-cardiac shunts are also at elevated risk for paradoxical embolism of air and/or thrombus [1, 9]. Awareness of the presence and severity of pulmonary hypertension prior to the anesthetic is critical. Children with pulmonary hypertension are at particular risk for adverse events in the operating room. This is due to the fact that patients in the operating room are more likely to experience episodes of hypoxia, hypercarbia, and acidosis during their anesthetic and surgical management which can act as powerful vasoconstrictors and potentially lead to a pulmonary hypertensive crisis [1].

The American Heart Association updated their guidelines in 2007 regarding the prevention of infective endocarditis. These guidelines have significantly reduced the frequency with which we administer perioperative antibiotics solely to decrease the risk of infective endocarditis [10]. In the event that it is necessary to administer antibiotics perioperatively to prevent infective endocarditis, effective communication between the critical care and the operating room teams is important to ensure compliance with the guidelines.

Finally, it is important for the anesthesia team to be aware of any conduction abnormalities a patient may have. The presence of a prolonged QT interval should be noted as inhalational anesthesia can act synergistically with other medications and potentially result in torsades de pointes [1]. It is also critical that the anesthesiologist is aware of the presence of a pacemaker or AICD as they can fail in the operating room – especially with the use of electrical cautery. A plan

for the management of this event should be in place prior to entering the operating room.

Endocrine

Major endocrine concerns that have an impact in the operating room include the management of patients on chronic steroid therapy and perioperative diabetes management. Patients on chronic steroid therapy and those with congenital adrenal insufficiency may be incapable of mounting a stress response when faced with stress, trauma, surgery, or illness. These children are commonly treated with corticosteroids perioperatively to prevent an Addisonian crisis [9]. There is no evidence to support this practice in the pediatric population [9], however, and a recent meta-analysis in the adult population without critical illness did not reveal adequate evidence for this practice as well [11]. One should consider the use of supplemental corticosteroids in the at-risk critically-ill population as these are the very patients who may experience hemodynamic instability when faced with the added stress of surgery. It has been recommended to administer the patient's daily dose of steroids on the day of surgery and give an additional "stress dose" to cover their needs but not increase the risk of negative side effects such as poor wound healing, inadequate glucose control, fluid retention, immunosuppression, and electrolyte imbalance [7]. von Ungern-Sternberg et al. have recommended a dose of 100 mg/m^2 on the day of surgery followed by 25 mg/m^2 every 6 h on the day of surgery, every 8 h on post-operative day #1, and every 12 h on post-operative day #2 [7]. The patient should be returned to their usual treatment dose on the third post-operative day.

Trauma, the stress of critical illness, and surgery can alter glucose homeostasis in a diabetic patient. The stress response can result in the secretion of catecholamines, cortisol, glucagon, and growth hormone which work to increase blood glucose by stimulating glycogenolysis and gluconeogenesis in the liver, promoting ketogenesis and lipolysis, and inhibit the uptake of glucose in muscle and fat. These patients are shifted into a catabolic state which can lead to significant hyperglycemia and potentially diabetic ketoacidosis [12]. The perioperative diabetic management plan should be made in concert with the pediatric intensivist and/or endocrinologist. These children should be evaluated clinically as well as biochemically. Often the issue leading to critical illness and surgery can cause metabolic decompensation, and if time allows, these patients should be corrected prior to going to the operating room [12]. However, if time does not permit preoperative correction, an insulin infusion and the rehydration process should be started promptly as these patients are often dehydrated. Type II diabetics on metformin should have it discontinued 24 h prior to surgery due to the risk of lactic acidosis [12].

Hematologic

Children with sickle-cell anemia are at increased risk for adverse events perioperatively. Sickling occurs in conditions of hypoxia, hypercarbia, acidosis, hypothermia, hypovolemia, and hypoperfusion states – all of which can occur in the operating room [1, 9]. To minimize these risks, these children who have significant anemia should undergo simple blood transfusion preoperatively. In the event these children will undergo complex or prolonged surgery, exchange transfusions should be considered as well. Generally, these children should have a hematocrit > 30 % and a HbS < 30 % prior to entering the operating room [1, 9]. They should also be adequately hydrated and active measures should be taken to warm them preoperatively. These preoperative measures will help circumvent postoperative morbidity.

Neurologic

Children with progressive peripheral neuromuscular disease are at increased risk perioperatively largely due to the concern of increased postoperative muscle weakness, especially as it relates to the child's baseline respiratory function. Careful discussion with the patient's family should occur prior to intubation (whether it occurs in the operating room or ICU) regarding the extubation plan, and the risk of that child remaining intubated/tracheostomy-dependent for a prolonged period of time. These children are also at increased risk of aspiration, and cardiac depression [1]. Their cardiorespiratory baseline with a recent echocardiogram and evaluation by a pediatric cardiologist should be established prior to exposing them to the cardiac depressant effects of anesthesia. When exposed to succinylcholine, a depolarizing muscle relaxant commonly administered in the operating room, these children are also at risk for life-threatening hyperkalemia and rhabdomyolysis.

Patients with a diagnosis of central core and multiminicore myopathies, Brody myopathy, and King-Denborough syndrome have an increased susceptibility of experiencing malignant hyperthermia (MH) if exposed to a triggering anesthetic (inhalational anesthesia and succinylcholine) as there appears to be a genetic link between these syndromes and MH [13]. The evidence linking MH susceptibility and other myotonias is varied depending on the molecular basis of the pathophysiology. There does not appear to be a relationship between mitochondrial myopathies and MH. Regardless, if there is a concern or a suspicion regarding a patient's susceptibility for MH secondary to a genetic syndrome or family history, it is imperative that this concern is communicated with the child's anesthesiologist to aid in the creation of a safe anesthetic plan for that patient.

Children with intracranial hypertension (secondary to hydrocephalus, a malfunctioning ventriculoperitoneal shunt, or brain tumor, for example) need to be identified prior to surgery as anesthetic agents have vasodilating properties and can acutely worsen their situation [1, 9]. Children on anticonvulsant therapy should ideally be optimized prior to the operating room. One should consider obtaining drug serum levels of these medications. As these agents typically have long half-lives, missing one dose is usually not problematic, however [9]. Depending upon the patient's condition, one may need to administer these medications intravenously.

Preoperative Testing

Although previously common practice, routine preoperative laboratory testing in the healthy child is no longer recommended. In the critically ill child, appropriate preoperative laboratory testing, evaluations, and consultations should be performed based on the patient's co-existing conditions and surgical procedure [7]. Any preoperative testing, and additional consultations should only be performed if anticipated benefits are believed to outweigh any risks involved [14]. For example, preoperative hemoglobin should be measured in infants, in children with a history of clinically significant anemia, in children whose disease process is associated with blood loss or a poor tolerance to anemia, and in those patients who are preparing to undergo a surgical procedure with a high risk of blood loss. Similarly, preoperative coagulation testing is useful in patients with a medical history consistent with a bleeding disorder, or in patients who are scheduled to undergo more complex surgery, such as neurosurgery, where the risks associated with minimal bleeding can be high. Analysis of a patient's serum electrolytes is necessary in those children who have an electrolyte imbalance such as those patients with renal insufficiency or with adrenal abnormalities, or in those patients who are on medications which might influence volume status and electrolyte balance [7]. Radiological studies (Chest X rays, airway and chest CT/MRI scans) are useful in children with airway or respiratory compromise, such as patients who present with a mediastinal mass. A preoperative cardiac evaluation including echocardiography is justified in those patients who have symptoms concerning for cardiac disease such as failure to thrive, low exercise tolerance, a pathologic-sounding murmur (e.g., louder than 2/6, diastolic, pansystolic, continuous), decreased femoral pulses and in the critically ill child, hemodynamic instability that is unexplained [1].

Adolescent females can be at risk for undetected pregnancy. When time permits, or when the critically ill adolescent female is preparing to undergo elective surgery, one should consider obtaining urine or serum beta-hCG level [14], particularly in situations in which the medical management of the patient would be altered by a positive result.

All preoperative laboratory testing should involve a risk/benefit analysis. If the test is to be performed, the results should affect a change in perioperative management. The risks of injury, discomfort, inconvenience, delay of surgery, or increased costs must be outweighed by a potential direct benefit to the patient [7].

Vascular Access

Appropriate intra-venous access is useful prior to surgery. The determination of what kind or how much access to attain is based on patient stability and anticipated fluid replacement and blood loss that will occur intra-operatively. Invasive arterial and/or central venous pressure monitoring is recommended in unstable patients undergoing complex procedures. Anesthesia providers are aware that access is easier to obtain on sedated or anesthetized children, so acquiring complete access prior to entry into the operating room is often not necessary, particularly in non-emergent situations. If a child is anticipated to be hospitalized for at least 4–7 days, the placement of a PICC line should be considered [15]. Schwengel et al. demonstrated that the preemptive placement of a PICC line in this patient population is associated with fewer venipunctures for blood sampling and replacement of failed peripheral IV catheters post-operatively. Due to the less frequent venipunctures, these patients experienced less pain during their hospitalization, and patient and parental satisfaction scores were subsequently higher. Although complications can occur with PICC placement, complications are less likely to occur with PICC lines when compared with other central venous catheters. Schwengel and her group advocate the placement of the PICC line intraoperatively to improve cost effectiveness.

Preventing Surgical Site Infections

Surgical site infections (SSIs) account for approximately 22 % of all nosocomial infections [16]. In pediatric patients, they prolong hospital stay by approximately 10 days and increase costs by more than $27,000 per patient [16]. Risk factors for surgical site infections include age, comorbidities (e.g., diabetes), obesity, tobacco abuse, malnutrition, steroid use, and immunosuppression [17]. It is estimated that up to 60 % of surgical site infections could be prevented using evidence-based strategies including appropriate antibiotic prophylaxis, enhanced oxygen administration, maintenance of perioperative normothermia, fluid management, and skin disinfection [16–18]. Not complying with these strategies is

associated with increased mortality – for example, a poor choice in antibiotic has been associated with a threefold increase in mortality, and hypothermia on arrival to the post-operative care unit has been associated with a greater than fourfold increase in mortality [18]. Unfortunately, compliance with guidelines has been suboptimal in many hospitals, and the etiology for this is believed to be multifactorial, with problems occurring at the patient, provider, and system levels [18].

Although pediatric-specific guidelines were not available, Ryckman et al. described the experience in which adult evidence-based data was applied to a pediatric setting to yield successful results in reducing SSIs [16]. This included building a specific process in which the appropriate antibiotic selection and dosing was consistently ordered in a timely fashion prior to each patient entering the operating room so that each patient could have the antibiotic administered prior to incision. In the critically-ill child preparing to undergo surgery, communication of who ordered, what dose, and timing of antibiotic administration is crucial in the fight against SSIs, especially considering that patients who undergo emergency surgery are at even higher risk of suffering from an SSI. In fact, team skills – namely, collaboration and communication, have been shown to be associated with decreased morbidity when analyzing high-risk medical settings such as intensive care units and the operating room [18].

Compliance with maintaining perioperative normothermia can also be difficult, particularly in the pediatric patient due to their increased body surface area. Intraoperative hypothermia is believed to be associated with a reduction in peripheral circulation, which may increase regional tissue hypoxia and make wounds more susceptible to infection, even when tissue contamination is low [19]. Additionally, it is difficult to maintain euthermia after anesthetic induction because all general anesthetics markedly disturb normal autonomic thermoregulation. In addition to the fact that patients are exposed to a cold operating environment, have potentially cold liquids on them that are allowed to evaporate, have heat loss from the surgical wound, and have a reduced metabolic rate under anesthesia, they also have impaired shivering and vasoconstriction due to the anesthetic [20]. It is not surprising then, that Meeks et al. demonstrated that patients with lower initial temperatures in the operating room were more likely to be hypothermic at the end of their surgery [18]. It has been suggested that preoperative warming the hour before surgery may be just as important in maintaining euthermia as the intraoperative and immediate postoperative periods to reduce rates of infection [19]. At our institution, all operating rooms are warmed during the night-shift. Additionally, all patients who are preparing to undergo surgery that is considered high-risk for surgical site infections (e.g., orthopedic spinal reconstruction and neurosurgical procedures) are warmed preoperatively using forced-air warming blankets [16].

Administration of supplemental oxygen at an FiO_2 of at least 0.6 both intra- and post-operatively is also useful in reducing surgical site infections. Developing and compliance with a standardized approach such as the use of a Surgical Site Infection (SSI) prevention bundle including (1) appropriate and timely antibiotic administration (2) maintenance of body temperature during surgery and (3) administration of supplemental oxygen during and for at least 4 h after surgery can significantly reduce the rate of surgical site infections.

Transportation of Critically Ill Patients

The act of transporting a critically ill child to his/her anesthetizing location carries risk in itself. During transport, the patient is removed from an advanced monitoring location to a situation in which such monitoring may not be easily available. Wallen et al. demonstrated that the intrahospital transport of critically ill children is associated with adverse events secondary to the transport process itself [21]. Namely, they found that intrahospital transport was significantly associated with significant changes in vital signs, alteration in ventilation and oxygenation, and equipment-related events. They showed that patients who have a higher degree of severity of illness, and a longer duration of transport are particularly at risk for adverse events. Mechanically ventilated patients were noted to have a higher frequency of mishaps compared to those who were not mechanically ventilated - likely secondary to the fact that mechanically ventilated patients have more equipment and can thus increase their chances of equipment-related adverse events.

It is imperative therefore, that patient's receive the same level of thorough care during the transportation process as they receive during their ICU stay and in the Operating Room itself. The most important issues of concern during the transportation process include "patency of the airway, preventing hypoxemia, protecting the airway from the aspiration of gastric contents, maintaining adequate circulation, protecting the patient from physical injury" [22], as well as the prevention of hypothermia [21]. Patients should receive the same level of monitoring during transport that they receive while in the ICU or in the OR. This meticulous level-of-care is particularly important in patients who are receiving vasoactive infusions. On transport, guard rails should be up, patients who need them should have physical restraints, and patients should be covered to prevent hypothermia as well as maintain patient dignity. Finally, emergency medications and equipment should be available throughout the transportation process [23].

Communication and Safe Hand-Off of Patient Care

Breakdowns in communication have been shown to result in patient injury, and are the second most common cause of inpatient surgical errors after technical errors [24]. Communication breakdowns have also been associated with delays in care, increased patient morbidity, and longer ICU stays [24, 25]. It is believed that acutely ill patients in surgical ICUs are the most vulnerable to communication errors [25]. According to Frei in an editorial regarding anesthetic risk, "Communication in a team is a function of the attitudes displayed, and attitude is a function of the value system of the individual. Although communication may function well amongst team members of the same profession, it is often under-utilized between colleagues from different specialty areas" [26]. Various medical specialties – Intensive Care, Surgery, Anesthesia, Cardiology, Radiology, and Hematology/Oncology, to name a few – should strive to align quality improvement efforts in improving cross-disciplinary communication.

An example of a process improvement initiative at Cincinnati Children's Hospital Medical Center to improve multi-disciplinary communication has been the "*Safe Hand-off of Patient Care*." The aim of this initiative was to ensure safe-handoff in patients presenting from the ICU to the operating room and vice-versa 100 % of the time [27]. To ensure the process is performed in a consistent manner, laminated cards are handed to all anesthesia personnel to aid in the post-operative hand-off process (Table 1.2). This checklist is easily adapted to the preoperative setting. In addition to the use of this simple tool, data on the hand-off process is regularly collected, and failures are discussed with providers in real-time so that behavior can be modified quickly.

Communication between health care providers, patients, and their families is also important – particularly in the critically-ill patient. Patient's families, and if age-appropriate, the patient himself should be provided appropriate information prior to surgery regarding prognosis and expected outcomes from surgery. This, of course, is inherent in the informed consent process. However, in the critically ill child, it is important that care providers from differing specialties (e.g., Critical Care, Surgery, and Anesthesia) agree and communicate the care plan to the patient and family. Patients who have Do Not Resuscitate (DNR) orders in place pose an ethical challenge prior to undergoing surgery and anesthesia. In 2008, the American Society of Anesthesiologists affirmed guidelines regarding the care of these patients. They encourage the communication amongst all parties that are involved in the care of the patient. In clinical situations in which there is time, the status of the DNR order should be reviewed with the family and with providers. Most families are not aware that the nature of modern anesthesia practice includes the use of vasoactive drugs, tracheal intubation, mechanical ventilation, and other "invasive" procedures [28] – a practice that could be considered "resuscitation" in other settings. The ASA guidelines suggest three possible outcomes to a review of the DNR order: (1) Full Attempt at Resuscitation in which there is a full suspension of the DNR order during the perioperative period; (2) Limited Attempt at Resuscitation Defined with Regard to Specific Procedures in which the family may elect or refuse to employ specific resuscitative measures during the perioperative period; and (3) Limited Attempt at Resuscitation Defined with Regard to the Patient's Goals and Values in which the family grants the anesthesiologist and surgeon permission to use their clinical judgment in accordance with the patient's and family's stated goals and values [29]. What constitutes "perioperative period" should also be clearly defined. Whatever decision is reached, a clear statement should be placed in the medical record regarding these preferences. As each patient, family, and clinical situation is unique, there is no single correct "solution" in these circumstances [28]. Only careful communication can ensure that each patient and family are treated with the dignity that they deserve during such a vulnerable time in their care.

Table 1.2 Cincinnati Children's Hospital Medical Center Department of Anesthesia handoff checklist

Handoff checklist
1. Stable airway/vital signs
2. Ask "Are you ready for report?"
3. Name, age, weight, allergies
4. Procedure
5. Relevant medical history
6. Type of airway management (ETT/LMA/Mask, awake/deep extubation?)
7. Access/fluids
8. Medications given
9. Intraoperative complications/issues?
10. Postoperative concerns (pain plan, labs, foreign bodies in airway)
11. Any questions?

Conclusion

Critically ill patients pose a major challenge as they transit through the care of multiple providers in the perioperative pathway. Thorough preoperative evaluation with identification of risk factors, optimization of these risk factors and adequate preparation of the patient, effective communication between care providers and the patient/families and amongst critical care unit and operating room teams and safe transport of these patients to and from the operating room are key factors to improving the outcome for the critically ill child requiring surgery.

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Frei FJ. Anaesthetists and perioperative risk. Paediatr Aanesth. 2000;10:349–51. With permission from John Wiley & Sons Inc.

Maxwell LG, Yaster M. Perioperative management issues in pediatric patients. Anesthesiol Clin North America. 2000;18(3):601–32. With permission from Elsevier.

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Pharmacology of Inhalational and Intravenous Anesthetic Agents

2

David P. Martin and Joseph D. Tobias

Abstract

Varying depths of sedation through general anesthesia may be required in critically ill patients during surgical interventions, non-invasive procedures such as magnetic resonance imaging, or invasive procedures such as central line placement. During such procedures, a variety of agents may be chosen to provide the conditions required for a surgical procedure including amnesia, analgesia, muscle relaxation and control of the sympathetic nervous system. The agents used for the induction and maintenance of general anesthesia may be broadly classified into either inhalational (volatile) or intravenous agents. In addition to their use in the operating room for the provision of general anesthesia, both the intravenous and volatile agents may be used outside of the operating for either their sedative properties or even occasionally for their therapeutic effects. Examples include the use of propofol for sedation during magnetic resonance imaging, pentobarbital to control intracranial pressure (ICP) in patients with traumatic brain injury, or the administration of isoflurane for the treatment of status asthmaticus. The following chapter reviews the history, pharmacology, and end-organ effects of the inhalational and intravenous anesthetic agents.

Keywords

Volatile agents • Intravenous anesthetic agents • Propofol • Etomidate • Ketamine • Barbiturates

Introduction

For major or minor surgical procedures, varying depths of sedation through general anesthesia may be required based on the surgical procedure and the patient's ability to cooperate. For infants and children, general anesthesia is frequently chosen as the optimal means of ensuring immobility and pain control during major surgical procedures. During such procedures, a variety of agents may be chosen to provide the conditions required for a surgical procedure including amnesia, analgesia, muscle relaxation and control of the sympathetic nervous system. The agents used for the induction and maintenance of general anesthesia may be broadly classified into either inhalational (volatile) or intravenous agents. The choice of the class of agent and the specific drug is broadly based on the patient's physical status and underlying co-morbid conditions, the clinical scenario, and the anesthesia provider's familiarity with the various agents. In addition to their use in the operating room for the provision of general anesthesia, many of these agents are used outside of the operating for either their sedative properties or even occasionally for their therapeutic effects. This may include the use of propofol for procedural sedation, the use of pentobarbital to control intracranial pressure (ICP) or the administration of isoflurane for the treatment of status asthmaticus. The following chapter reviews the history, pharmacology, and end-organ effects of the various inhalational and intravenous anesthetic agents.

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The Inhalational Anesthetic Agents

The inhalational anesthetic agents include nitrous oxide (N_2O) and the five potent inhalational agents (halothane, enflurane, isoflurane, sevoflurane, and desflurane). The potent inhalational anesthetic agents, otherwise known as volatile agents include halothane, enflurane, isoflurane, sevoflurane and desflurane. These agents will discussed together and their individual differences highlighted later on in this chapter.

Nitrous Oxide

N_2O is the oldest of the inhalational anesthetic agents. Unlike the volatile agents that are delivered using a vaporizer (see below), N_2O is delivered from a tank (E cylinder) like other medical gases such as oxygen. Although there has been a decline in its use with the introduction of volatile agents with low blood-gas solubility coefficients (desflurane, sevoflurane), N_2O is still available in the majority of the operating rooms throughout the world. Additionally, it has been used outside of the operating room for procedural sedation for decades and in some centers, practitioners have found a renewed interest in its use for this purpose.

N_2O is colorless and depending on the source, has been described as either sweet smelling or odorless. In clinical practice, N_2O is administered with oxygen in concentrations varying from 30 % up to 70 % to provide sedation/analgesia or a weak anesthetic effect. In concentrations of 70 % with 30 % oxygen, N_2O will render the majority of patients amnestic and provide moderate levels of analgesia sufficient for minor surgical procedures. In the arena of procedural sedation N_2O can be combined with a topical anesthetic for short, minimally invasive procedures such as venipuncture or lumbar puncture. Prior to the advent of the new era of inhalational anesthetic agents, N_2O was also used during inhalational inductions because it enhanced the speed of induction. The speed of induction is increased by the co-administration of N_2O because it is a fast acting anesthetic on its own, and secondly, because of the "second gas effect". As N_2O is absorbed into the blood from the alveoli, it effectively results in a concentration increase in the remaining gases present in the alveoli. This creates a larger concentration gradient between the alveoli and blood, thus a faster time to unconsciousness. This same principle results in what is known as diffusion hypoxemia during recovery from N_2O sedation. As the N_2O diffuses from the blood into the alveoli, its alveolar concentration increases quickly thereby decreasing the alveolar concentration of oxygen.

Chronic exposure to N_2O can lead to an impairment of bone marrow function and anemia by inactivation of methionine synthetase, an enzyme necessary for vitamin B_{12} metabolism. The anemia is typically described as megaloblastic. Because there is impairment of DNA synthesis with vitamin B_{12} deficiency, there is cell growth without cell division, thus leading to macrocytic red blood cells. This same effect on vitamin B_{12} metabolism can, with repeated or prolonged exposure, lead to neurological signs and symptoms with deterioration of the posterior columns of the spinal cord. The risk of neuropathy is enhanced in patients with subclinical B_{12} deficiency. N_2O diffuses into and expands gas-containing closed spaces in the body (obstructed bowel, pneumothorax, middle ear, pneumocephalus, and air emboli) because it is significantly more soluble in blood than nitrogen. With time, the pressure in the closed cavity and size of the cavity can increase to dangerous levels with resultant physiologic changes based on the site of accumulation.

Because of its low potency, nitrous oxide must be delivered in concentrations in excess of 50–70 % to achieve an amnestic or analgesic effect. This combined with the potential for end-organ toxicity with prolonged exposure excludes its use for prolonged periods of time. Given these issues, it has a limited role in the PICU and its major role outside of the operating room remains in the arena of procedural sedation. As such, it will not be discussed in further detail in this chapter.

Volatile Anesthetics

History of the Volatile Agents

The practice of inhalational anesthesia began in the 1840s with the demonstration of the efficacy of diethyl ether by Crawford Long (ether dome demonstration) and WTG Morton. Although these agents provided the needed components for surgical anesthesia, adverse effects were soon noted with the first generation of the inhalational anesthetic agents, including flammability, adverse end-organ effects, and unfavorable pharmacokinetics with prolonged postoperative effects. Subsequent advancements in fluorine chemistry and the development of efficient and cost-effective ways of incorporating fluorine into the chemical structure of various molecules led to the next generation of inhalational anesthesia which included agents such as chloroform and trichloroethylene [1]. Although less flammable than their predecessors, these agents still had significant adverse effects, including hepatotoxicity and neurotoxicity as well as unfavorable pharmacokinetics resulting in prolonged recovering times.

The next advancement was the development of various fluorinated hydrocarbons in the 1940s [2]. This work led to the synthesis in the early 1950s of fluroxene (2,2,2-trifluoroethyl vinyl ether), a fluorinated hydrocarbon, which was the first of this class of agents to be widely used in clinical practice [2, 3]. Despite advantages over the previously available

inhalational anesthetic agents, fluroxene's adverse effect profile included arrhythmias, nausea and vomiting, and hepatotoxicity [3–5]. Halothane, a halogenated alkane, was introduced into clinical practice in 1956 [6]. When compared with its predecessors, halothane offered several favorable properties including non-flammability, a favorable blood:gas partition coefficient, a favorable profile for inhalation induction including a rapid onset and limited pungency, bronchodilatation, relative cardiovascular stability, and a decreased incidence of nausea and vomiting. Halothane became the mainstay of inhalational anesthesia for the next 20 years. However, halothane's potential to elicit an immune-mediated hepatotoxicity especially in the adult population pushed the development of additional agents with decreased metabolism, less risk of hepatotoxicity, and a better safety profile. Ongoing research in the area of inhalational anesthesia over the next 20 years led to the development of the substituted methyl-ethyl ethers. The substitution of fluorine for the various halides surrounding the carbon atoms led to greater stability and lower tissue solubility. This work led to the development of the modern class of inhalational anesthetic agents including enflurane, isoflurane and eventually desflurane. The latter two agents combined with the reintroduction of sevoflurane, a methyl-isopropyl either, into clinical practice in the early 1990s comprise the currently used class of potent inhalational anesthetic agents.

Chemical Structure and Physical Characteristics

The volatile agents are two chemically distinct classes (alkanes and ethers) with similar hypnotic and anesthetic properties. Halothane is an alkane (a two carbon chain) while the other four agents (enflurane, isoflurane, desflurane, and sevoflurane) are ethers. Although these agents share a similar physiologic effect (production of a general anesthetic state), their physical effects (blood:gas solubility, blood:fat solubility, and potency) vary based on the substitution of various halides (chloride, bromide, fluouride) for hydrogen atoms around the carbon chain.

The potent inhalational anesthetic agents are volatile liquids which mean that they will revert to the gas phase at atmospheric pressure and room temperature. As such, they are administered to the patient via a vaporizer that is situated on the anesthesia machine. The vaporizers allow the anesthesia provider to increase or decrease the inspired concentration of the agent by turning the dial on the device. As the concentration on the vaporizer is increased, more of the fresh gas flow from the anesthesia machine is diverted into the vaporizer thereby increasing the output of the agent and its inspired concentration. Because the vapor pressures of the volatile anesthetic agents vary, there is a specific vaporizer for each agent. The volatile agents are monitored by sampling the gas in expiration and inspiration. The end-tidal or expired concentration has been shown to correlate with the alveolar concentration [7]. The end-tidal concentration is used clinically, along with many other signs and monitors, to judge the approximate depth of anesthesia.

Uptake and Distribution of the Volatile Agents

The inhalational agents are delivered via the respiratory system, thereby resulting in unique qualities when compared to intravenous agents. Delivery, uptake, distribution, and elimination are governed by principles that differ from intravenous agents used in the critically ill PICU patient. One of the primary characteristics which determines the onset and duration of action of a potent inhalational anesthetic agent is the blood:gas solubility coefficient. This coefficient defines the solubility of the agent in the blood and determines the concentration ratio between the blood and the alveolar gas when equilibrium is reached.

A basic premise to understanding the onset of these agents is the assumption that the alveolar concentration of the agent equals the brain concentration. A low solubility in the blood (low blood:gas partition coefficient) allows the alveolar concentration of the agent and hence the brain concentration of the agent to increase more rapidly than agents with a higher solubility in blood. The same is true in regards to the dissipation of the effects when the agent is discontinued. Although this difference is most notable during the induction of anesthesia, the depth of anesthesia can also be adjusted more quickly with an agent that has a lower blood:gas partition coefficient. Desflurane has the lowest blood:gas solubility coefficient and therefore the most rapid onset and offset of activity, followed in order by sevoflurane, isoflurane, enflurane, and halothane (Table 2.1). Due to the rapidly increasing number of surgical cases performed on an outpatient basis, the volatile agents have evolved significantly since their advent more than 150 years ago. Agents with lower blood:gas partition coefficients such as desflurane and sevoflurane

Table 2.1 Physical characteristics of the potent inhalational anesthetic agents

Volatile agent	Vapor pressure (mmHg at 20 °C)	Blood: gas partition coefficient	Minimum alveolar concentration or MAC (%)
Halothane	243	2.54	0.76
Enflurane	175	1.91	1.7
Isoflurane	238	1.46	1.2
Sevoflurane	160	0.69	2
Desflurane	664	0.42	6

allow for a much more rapid wake-up, fewer prolonged residual effects, and potentially fewer adverse effects which provide significant patient and healthcare (cost) benefits for the increasing outpatient surgical population.

In addition to the blood:gas partition coefficient, the increase in the alveolar concentration of the agent is determined by their delivery to the alveolus. The rapidity with which the alveolar concentration increases is an effect of both the minute ventilation and the inspired concentration of the agent. Following delivery, the inhalational anesthetic agents are then taken up from the alveoli into the blood. Uptake is dependent on the agent's solubility in the blood (blood:gas partition coefficient), blood flow through the lungs (cardiac output), distribution of blood flow to the various tissue beds, and the solubility of the agents in these tissues (blood:tissue solubility coefficient). The end-capillary venous blood from the lungs which empties into the left atrium and eventually becomes the arterial blood leaving the left ventricle rapidly equilibrates with the alveolar concentration [7]. This latter principles explains the premise that the alveolar concentration of the agent parallels the brain tissue concentration. These principles describe why insoluble agents (desflurane and sevoflurane) with a low blood:gas partition coefficient result in a more rapid rise in the alveolar concentration and therefore the most rapid onset of action.

Patient factors may also affect the increase in the alveolar concentration and hence the onset of action of the volatile agents. Alterations in the onset of action may be seen in patients with ventilation-perfusion mismatch or with true shunt related to congenital heart disease. In a patient with a left-to-right shunt, blood with a high concentration of the inhalational anesthetic agent returns from the lung and enters the left atrium. Some portion of this blood (based on the Qp/Qs ratio) recirculates through the lungs via the left-to-right shunt. This results in an increase in the mixed venous concentration of the inhalational anesthetic agent more rapidly than the normal. This accelerates the increase of the alveolar concentration and thereby the onset of action of the agent. In a patient with a right-to-left shunt, the opposite effect occurs with a delayed onset of action of these agents.

Minimum Alveolar Concentration of the Volatile Agents

The potency of the inhalational anesthetic agents is measured using the principle known as minimum alveolar concentration (MAC). MAC is the end-tidal concentration (percentage) of the volatile agent that prevents 50 % of patients from moving in response to a surgical stimulus. The most potent of the agents will have the lowest MAC value as less is required to produce a given clinical effect. Halothane has a MAC of approximately 0.76 % while desflurane is the least potent with a MAC of 6 % (Table 2.1). Several factors including age, co-morbid conditions, and the concomitant administration of other medications affect MAC. The opioids, α_2-adrenergic agonists, propofol, barbiturates, and benzodiazepines lower the MAC of the volatile agents. Other factors affecting MAC include age, pregnancy, and central nervous system disorders. MAC is low in preterm infants, increases in term infants, and then decreases slightly with advancing age [8, 9].

End-Organ Effects

Despite their use in clinical anesthetic practice for over 150 years, the exact cellular mechanism responsible for the general anesthetic effects of these agents has not been fully identified. Current theories regarding their mechanism of action suggest that they stabilize critical proteins including receptors of inhibitory neurotransmitters such as γ-amino butyric acid (GABA). Because the potency of each volatile agent correlates with their solubility in oil, it is theorized that the anesthetic effect involves interaction with a hydrophobic substrate. The current consensus is that volatile anesthetics do not act by a single mechanism. A location of action within the spinal cord may explain skeletal muscle relaxation while a cortical site explains sedation and hypnosis.

CNS Effects

In addition to their anesthetic properties, the volatile agents cause a dose-related decrease in CNS activity, reduction of the cerebral metabolic for oxygen ($CMRO_2$), and depression of electroencephalographic (EEG) activity. In large enough concentrations, an isoelectric EEG will occur. In contrast to their usual depressant effects on the EEG pattern, in specific circumstances, both enflurane and sevoflurane can activate the EEG and produce EEG evidence of epileptiform activity [10]. EEG activation occurs most commonly during anesthetic induction when there is a rapid increase in the alveolar concentration of the agent or with the administration of high inhaled concentrations. EEG activation is enhanced by hyperventilation and the development of hypocarbia. Despite this property, the volatile agents including sevoflurane depress EEG activity and have been used in the treatment of status epilepticus [11, 12].

The volatile agents decrease the $CMRO_2$; however, they increase cerebral blood flow (CBF) in a dose-dependent manner via a reduction in cerebral vascular resistance. The cerebral vasodilatation induced by the volatile agents may elevate intracranial pressure (ICP) in patients with compromised intracranial compliance. In these patients, cerebral perfusion pressure (CPP) may decrease not only due to the increase in ICP, but also the hemodynamic effects which result in a lowering of mean arterial pressure (MAP) [13]. The adverse effects on ICP vary from agent to agent, are least with isoflurane, and can be minimized by limiting the concentration to 1.0 MAC or blunted by hyperventilation to induce hypocarbia ($PaCO_2$ of 25–30 mmHg) [14, 15].

Cardiovascular Effects

In the practice of pediatric anesthesia, anesthesia is frequently induced by the inhalation of increasing concentrations of a volatile agent to avoid the need for placement of intravenous access in an awake child. Prior to the introduction of sevoflurane into clinical practice, halothane was the time-honored agent for the inhalational induction of anesthesia given its lack of irritant effects on the airway. However, especially in small infants or patients with co-morbid conditions, the potent negative inotropic and negative chronotropic effects of halothane remained the number one cause of perioperative cardiac arrest in infants and children [16]. Given its limited effects on myocardial contractility and chronotropic function when compared with halothane, sevoflurane became the preferred agent for the inhalational induction of anesthesia with the eventual removal of halothane from anesthetic practice. Aside from the issues of perioperative cardiac arrest, the volatile agents generally share hemodynamic effects including a decrease of MAP, depression of myocardial contractility, and a reduction of myocardial oxygen consumption. These effects are modified by several factors including co-morbid cardiovascular diseases, the concomitant administration of other medications, and the patient's intravascular status.

Although the volatile agents as a group result in a general depression of hemodynamic and cardiovascular function, the specific changes in cardiac output, systemic vascular resistance, and heart rate vary to some respect from agent to agent. Isoflurane and desflurane result primarily in a decrease in systemic vascular resistance and MAP. The vasodilatation results in reflex tachycardia and in general, an increase in cardiac output. A rapid increase in the inspired concentration of desflurane also stimulates the sympathetic nervous system and thereby further increases heart rate. A decrease in heart rate is commonly seen with sevoflurane administered at lower inspired concentrations (0.5–1 MAC) while inspired concentrations greater than 1–1.5 MAC may decrease SVR and result in a mild reflex tachycardia. Although the negative chronotropic effects of sevoflurane are generally less than those seen with halothane, profound bradycardia has been described during inhalational induction with sevoflurane in patients with trisomy 21 [17, 18]. Halothane on the other hand has little or no effect on SVR and results primarily in direct negative chronotropic and inotropic effects. Given the concerns surrounding halothane, it has been removed from the US market.

The reflex tachycardia which occurs with isoflurane and desflurane can increase myocardial oxygen demand while vasodilatation may lower diastolic blood pressure thereby reducing myocardial perfusion pressure and myocardial oxygen delivery. The imbalance that may occur between myocardial oxygen delivery and consumption has led to theoretical concerns regarding the potential for myocardial ischemia. Additionally, vasodilatation of the normal coronary vasculature with no effect in areas of fixed coronary stenosis may result in a coronary steal phenomenon. Due to these concerns, isoflurane and desflurane should be used cautiously in patients at risk for myocardial ischemia or in patients who are unable to tolerate tachycardia and a decrease in systemic vascular resistance. This may also be a consideration in patients with residual or palliated congenital heart disease in whom alterations in the systemic and pulmonary vascular resistance may significantly affect the ratio of pulmonary to systemic blood flow.

Respiratory Effects

The inhalational anesthetic agents also result in a dose-dependent depression of ventilatory function. With an increasing inspired concentration and anesthetic depth, there is a rightward shift of the CO_2 response curve with a progressive decrease in alveolar ventilation characterized by a reduction in tidal volume and an increase in $PaCO_2$ in spontaneously breathing patients. The volatile agents also blunt the normal ventilatory responses to hypercarbia and hypoxia. These agents may further impair oxygenation especially in patients with pulmonary parenchymal disease or atelectasis through the inhibition of hypoxic pulmonary vasoconstriction (HPV) [19]. As with many of the other physiologic effects, the impact on HPV and hence oxygenation is dose dependent with limited effects at a concentration ≤ 1 MAC. Beneficial effects on the airways include a direct effect on bronchial smooth muscle with a decrease in the cytoplasmic calcium availability and bronchodilatation [20]. Given this effect, the inhalational anesthetic agents have been used effectively outside of the OR for the treatment of patients with refractory status asthmaticus [21, 22]. Airway effects result from both a depression of airway reflexes and a direct effects on the airway smooth musculature [23, 24].

Hepatic Effects

In addition to their direct effects, secondary effects may occur from the metabolic products of the volatile agents. In general, the newer agents have been developed to undergo little or no metabolism thereby limiting the potential adverse effects related to their metabolic products. Fifteen to 20 % of halothane is recovered as metabolites compared to 3–5 % for sevoflurane, 2–3 % for enflurane, 0.2 % for isoflurane, and less than 0.1 % for desflurane. A significant concern with the older volatile agents including halothane was the development of hepatotoxicity. Although described shortly after the introduction of these drugs into clinical practice, the mechanism of the hepatic injury was later determined to be related to an immune-mediated reaction [25–28]. The metabolic product, trifluroacetic acid (TFA), acts as a hapten, binding to hepatocytes and thereby inducing an immune-mediated hepatitis. The diagnosis of hepatic injury following inhalational anesthetic agent use can be confirmed by the demonstration of the anti-TFA antibody in the sera of patients.

Although described primarily with halothane, given its higher metabolic processing with a greater production of TFA, there have been anecdotal reports of hepatitis with enflurane, isoflurane, and even desflurane [28–30]. The metabolic pathway of sevoflurane is different from the other volatile agents and does not result in the production of TFA with no risk of the hepatoxicity.

Hepatotoxicity from the volatile agents manifests as either a mild or a fulminant form. As the incidence of hepatotoxicity is highest with halothane, the majority of the information regarding hepatotoxicity from the volatile agents is related to halothane. Hepatoxicity is most common in adult patients who are 35 years of age or more. The mild form affects 20 % of adults who receive halothane while the fulminant form (halothane hepatitis) occurs in 1 of every 10,000 adult patients following halothane anesthesia. The fulminant form results in massive hepatic necrosis with hepatic insufficiency or failure resulting in a mortality rate of 50–75 %. The majority of the patients (up to 95 %) who develop the fulminant form have had a prior exposure to halothane. Additional risk factors include female gender, middle age, obesity, and factors which induce the hepatic microsomal enzymes such as chronic ethanol ingestion and medications such as isoniazed and the barbiturates. Given the concerns of halothane hepatitis, there was limited use of this agent in the adult population following the introduction of isoflurane and enflurane into clinical practice. Until the early 1990s when sevoflurane was introduced, it remained the most commonly used inhalational agent in infants and children as hepatitis is exceedingly uncommon with an incidence of less than 1/200,000 [31, 32].

Renal Effects

In rare instances, nephrotoxic effects may occur with the volatile agents related either to release of fluoride during the metabolism of the parent compound or the production of toxic metabolic byproducts. The volatile agents are highly substituted around their carbon atoms with fluoride. Therefore, dependent on their metabolic fate, the dose administered and its duration, fluoride may be released. Fluoride concentrations greater than 50 μmol/L can result in decreased glomerular filtration rate or nephrogenic diabetes insipidus. Methoxyflurane, which is highly substituted with fluoride and metabolized, was eliminated from clinical practice due to its potential for nephrotoxicity. Issues with potential fluoride effects have also been noted with enflurane especially during prolonged administration. Although less enflurane is metabolized than methoxyflurane, its content of fluoride is high enough that serum fluoride concentrations can increase with prolonged administration [33].

Concerns regarding the potential nephrotoxicity of sevoflurane, noted in the literature, include not only fluoride release during metabolism and, but also the production of the metabolic byproduct, compound A. Although high levels of serum fluoride have been noted following the prolonged administration of sevoflurane, clinical signs of nephrotoxicity are extremely rare. The low blood:gas partition coefficient of sevoflurane results in its rapid elimination from the body and sevoflurane unlike methoxyflurane does not undergo metabolism in the kidney, but only in the liver. Therefore, unlike methoxyflurane, there is no local renal release of fluoride.

The second concern raised regarding potential nephrotoxicity of sevoflurane is related to the production of a unique metabolite, compound A. Compound A is produced during the metabolism of sevoflurane and its reaction with the CO_2 soda lime in the carbon dioxide absorber of the anesthesia machine [34, 35]. To date, the majority of information concerning compound A and its potential toxicities is from animal studies. As such the toxic concentration of compound A and the mechanism of renal injury in humans is unknown [36]. High compound A concentrations occur in the setting of a high inspired concentration of sevoflurane, a low fresh gas flow of less than 2 l/min through the anesthesia circuit system, increasing temperatures of the soda lime canister, decreased water content of the CO_2 absorbent, and high concentrations of potassium or sodium hydroxides in the CO_2 absorbent. To date, it appears that the potential nephrotoxicity of compound A has been exaggerated as the clinical data have failed to show any alteration in renal function even in adults with pre-existing renal dysfunction.

Malignant Hyperthermia

In addition to specific end-organ effects, rare idiosyncratic reactions may be seen with the volatile agents including malignant hyperthermia (MH). Although uncommon, it is potentially the most lethal of all of the adverse effects that can occur with the volatile agents. MH is an inherited disorder of muscle metabolism with an estimated incidence of 1:15–20,000 in adults and 1:50,000 in infants and children. It can be triggered by any of the volatile agents. The primary cellular defect resides in the ryanodine calcium channel in the sarcoplasmic reticulum (SR). Dysfunction of this ion channel following exposure to a volatile agent results in the exaggerated and continued release of calcium from the SR into the cytoplasm. The ongoing increase in cytoplasmic calcium results in skeletal muscle contraction and a hypermetabolic state. Clinical signs and symptoms include tachycardia, hyperthermia, hypercarbia, muscle rigidity, and rhabdomyolysis. Rhabdomyolysis with muscle breakdown results in hyperkalemia and acidosis. Treatment includes prompt recognition, removal of the triggering agent, and the administration of dantrolene. Additional therapy is aimed at the correction of the metabolic disturbances (hyperkalemia and acidosis), external cooling, and maintenance of diuresis to limit the impact of the myoglobinuria on renal function. Without appropriate therapy including the administration of dantrolene, mortality exceeds 90 %.

Intravenous Anesthetic Agents

In the operating room, the intravenous anesthetic agents are administered as premedicants to alleviate preoperative anxiety and to induce or maintain general anesthesia. Outside of the operating room these agents are used for sedation and anxiolysis during invasive or non-invasive procedures. Commonly used intravenous anesthetic agents include the barbiturates (thiopental, thiamylal, and pentobarbital); propofol, an alkylphenol; etomidate, an imidazole; ketamine, an arylcyclohexylamine; and midazolam, a benzodiazepine. As with any agent used in the PICU, these agents have specific effects on hemodynamic and respiratory function as well as other agent-specific concerns which must be considered when choosing the most appropriate agent for the various clinical scenarios. Although any of these agents can be used to induce anesthesia and begin the anesthetic process, the specific choice of the agent and its dose is based on the clinical scenario, the anticipated duration of the surgical procedure, and the patient's underlying hemodynamic status and co-morbid conditions. These medications are generally administered in combination with other intravenous or volatile agents to produce analgesia, hypnosis, amnesia, and muscle relaxation.

The intravenous anesthetic agents produce their effects by either enhancing inhibitory neurotransmission or inhibiting excitatory neurotransmission. The predominant inhibitory neurotransmitter in the central nervous system is γ-aminobutyric acid (GABA) whereas the predominant excitatory neurotransmitter is glutamate which acts via the N-methyl-D-aspartate (NMDA) receptor. A GABA molecule binding to its receptor in the extracellular position results in increased chloride ion conductance and a decrease of the resting membrane potential (RMP) resulting in hyperpolarization [37]. Thiopental, midazolam, propofol, and etomidate interact with different components of the $GABA_A$ receptor complex to enhance the function of the inhibitory neurotransmitter system GABA [38–41]. Ketamine acts differently by blocking open channels of NMDA receptors that have been activated by glutamate, an excitatory transmitter, and interacting with brain acetylcholine to create a dissociation between the thalamocortical and limbic systems [42–44]. The NMDA receptor acts in an excitatory fashion in the central nervous system. The receptor has both ligand gated and voltage gated properties. The receptor is modulated by ligands such as magnesium, glutamic acid, and glycine.

Barbiturates

The barbiturates were first synthesized in 1864 by von Baeyer. Thiopental, a short acting barbiturate was first administered for clinical use in 1934 by Lundy at the Mayo Clinic. The first widespread use of thiopental was for the induction of anesthesia in trauma patients during World War II. The high incidence of death in these patients who were frequently hypovolemic from traumatic injuries led some to suggest that the use of the barbiturates should be discontinued in anesthetic practice. Despite the initial issues, the barbiturates were commonly used for anesthetic induction until the early 1990s when they were slowly replaced by propofol. The short acting agents of the barbiturate class including thiopental are no longer available in the United States. Although still manufactured in some European countries, thiopental and thiamylal are not exported to the United States as this class of agent was used for lethal injection (death penalty).

The barbiturates can be classified according to their chemical structure or their duration of activity. The chemical structure of the barbiturates varies in that their ring structure can contain a sulfur atom (thiobarbiturates such as thiamylal and thiopental) or an oxygen atom (oxybarbiturates or methohexital). A sulfur atom in the ring results in a more rapid onset and a shorter duration of action. Increasing the length of the carbon side-chains at position 5 of the ring increases the potency of the compound. Short acting agents such as methohexital, thiopental, and thiamylal have a clinical duration of action of 5–10 min and are used most commonly as a single bolus dose for the induction of anesthesia. The clinical effects of the short acting agents dissipate rapidly related to their redistribution, although their hepatic metabolism may take hours. When a more prolonged effect is needed, a continuous infusion may be used to maintain constant plasma levels. However, the offset time will also be markedly prolonged and dependent on the duration of the infusion.

Long acting agents with half-lives of 6–12 h include pentobarbital and phenobarbital. In the PICU setting, the barbiturates have occasionally been used by continuous infusion for sedation during mechanical ventilation or more commonly, as therapeutic agents to suppress seizures or to decrease ICP in patients with traumatic brain injury [45–50]. All of the barbiturates (except phenobarbital) undergo hepatic metabolism. Oxidation is the most important pathway with the production of charged alcohols, ketones, phenols, or carboxylic acids. These metabolites are readily excreted in the urine or as glucuronic acid conjugates in the bile. Renal excretion is important in the elimination of phenobarbital, accounting for a large amount of its elimination in an unchanged form. The alkalinization of urine enhances the renal excretion of phenobarbital. Given its dependency on renal elimination, dosing alterations may be required in patients with altered renal function. The induction or stimulation of hepatic enzymes by the barbiturates is responsible for the recommendation that they not be administered to patients with acute intermittent porphyria. In this setting, they may precipitate an attack by stimulating γ-aminolevulinic acid synthetase, the enzyme responsible for the production of porphyrins.

The ultra-shorting acting barbiturates (thiopental and thiamylal) are used clinically in a 2.5 % solution with a pH 10.5. The high pH results in a bacteriostatic solution, limiting concerns of bacterial contamination as well as limiting the pain with intravenous injection. However, the pH of 10.5 leads to incompatibilities with other medications and parenteral alimentation solutions thereby necessitating a separate infusion site if a continuous infusion is used in the PICU setting. Of additional concern is the formation of a precipitate when the barbiturates are administered with drugs such as rocuronium mandating flushing the line during rapid sequence intubation of the trachea. Failure to do so may result in a precipitate and loss of intravenous access during critical moments. Local erythema, thrombophlebitis, or skin sloughing may occur with subcutaneous infiltration. The barbiturates possess no analgesic properties and therefore should be used with an opioid in situations requiring analgesia.

Like propofol and most other anesthetic agents, the effects of the barbiturates on hemodynamic and respiratory function are dose-dependant. In healthy patients, sedative doses will have limited effects on cardiovascular function, central respiratory drive, and airway protective reflexes while larger doses may result in respiratory depression, apnea or hypotension. The effects on cardiovascular and ventilatory function are additive with other sedative and analgesic agents. Hypotension results from various effects on the myocardium, peripheral vasculature and sympathetic nervous system including peripheral vasodilation, a direct negative inotropic effect, and blunting of catecholamine release. On a cellular level, the barbiturates inhibit calcium fluxes across cell membranes and from the sarcoplasmic reticulum thereby depressing myocardial contractility. With the introduction of new pharmacologic agents in the PICU and the operating room as well as acquisition issues, the use of the barbiturates for sedation during mechanical ventilation and for the induction of anesthesia has dramatically decreased. In addition to their role for therapeutic agents or perhaps for the provision of sedation during mechanical ventilation, there are several reports outlining their use for procedural sedation especially during non-painful, radiologic imaging. In particular, the short-acting oxybarbiturate, methohexital, has been used extensively via both the oral and PR route (rectal dose of 20–30 mg/kg) as a sedative for CT or MR imaging with reported success rates of up to 80–85 % [51]. The onset of sleep is rapid (6–10 min) with a duration of effect of 1.5–2 h. Adverse effects are uncommon with mild respiratory depression responsive to repositioning or the administration of supplemental oxygen occurring in up to 4 % of patients. Unlike the other barbiturates, methohexital may activate the EEG and precipitate seizures in patients with underlying seizure disorders. Although generally administered intravenously, thiopental has also been used as a rectal agent for sedation for radiologic procedures in doses of 25–50 mg/kg [52, 53]. Pentobarbital has an intermediate duration of action and remains a popular choice for intravenous sedation during radiologic procedures such as MR imaging where sedation times may approach 60–90 min which allows the completion of most MR studies. Although pentobarbital may be administered via multiple routes (IV, IM, and enteral), IV administration remains the most commonly used route. Pentobarbital is administered in increments of 1–2 mg/kg every 3–5 min until sleep is induced (average total dose 4–5 mg/kg). Respiratory depression and hypotension may occur, especially with rapid intravenous administration. Disadvantages with pentobarbital include prolonged recovery times (2–4 h) and emergence issues including agitation. The latter has been treated effectively with both oral and intravenous caffeine [54].

Propofol

First introduced in the early 1970s, propofol was discovered while investigating substituted phenol compounds [55]. Due to propofol's insolubility in water, it has been packaged in different lipophilic moieties. The current formulation consists of 1 % (10 mg/mL) propofol with the addition of soybean oil, glycerol, and purified egg phosphatide to increase solubility. Because microbial growth is possible in the emulsion, ethylenediaminetetraacetic acid (EDTA) was subsequently added as a preservative to prevent bacterial growth. The formulation's pH is near-neutral and it appears as a slightly viscous, milky white, substance. Propofol is also available as a 2 % solution and as the water soluble pro-drug, fospropofol. The 2 % solution is not available in the United States while the latter has not seen significant clinical use in the pediatric population [56].

Propofol (2,6-diisopropylphenol) is an alkyl-phenol (oil at room temperature) compound with general anesthetic properties. Although it has a chemical structure that is distinct from other intravenous anesthetics, its mechanism of action is similar as it acts through the GABA system [37, 57]. Propofol facilitates the binding of the native GABA neurotransmitter to membrane-bound receptors. Although propofol was initially introduced into anesthesia practice for the induction and maintenance of anesthesia, its rapid onset, recovery times, and ease of use led to its eventual use for sedation in a variety of settings including ICU and ambulatory settings [58–60]. These properties also make propofol an attractive choice for short-term sedation during procedures.

Propofol is metabolized in the liver via conjugation to glucuronide and sulfate producing compounds that are water-soluble and thus excreted renally [61]. There are minimal unchanged fractions of the drug excreted in the urine and

feces. There is debate concerning the extent and presence of extrahepatic metabolism of the drug [62]. Extrahepatic metabolism is suggested due to the fact clearance of the drug exceeds hepatic blood flow. Propofol exhibits a very rapid redistribution from the central, highly perfused, compartment to more lipid-rich and less well perfused body compartment with an initial redistribution half-life of 2–8 min. With repeated doses or as the drug is continuously infused, the other compartments reach equilibrium with the central compartment and there is context-sensitive half-life such that the recovery time may be longer after prolonged infusion.

Propofol's cardiovascular effects resemble those of the barbiturates with the potential for hypotension from peripheral vasodilation and negative inotropic properties. The net result is a combination of decreases in preload and contractility. These effects are dose-dependent and can be accentuated following rapid bolus administration, in patients with compromised cardiovascular function, or in hypovolemic patients. The peripheral vasodilatation may be particularly detrimental in patients with a fixed stroke volume such as those with aortic or mitral stenosis. The adverse hemodynamic consequences of propofol administration can be prevented by the administration of calcium chloride which attenuates the changes in contractility and systemic vascular resistance (SVR) [63]. Other methods used to avoid hemodynamic instability with propofol include assuring euvolemia prior to induction, coadministration of an alpha$_1$-agonist such as phenyephrine and slow administration during induction. Additional cardiovascular effects may be caused by augmentation of central vagal tone leading to bradycardia, conduction disturbances, and asystole [64–66]. These effects are more likely with the concomitant administration of other medications known to alter cardiac chronotropic function including fentanyl, succinylcholine, or antiarrhythmic medications.

Beneficial effects on airway resistance and compliance have been noted when propofol is used as an induction agent in patients with preexisting airway hyper reactivity. When comparing the effects of anesthetic induction with equipotent doses of propofol, etomidate, or thiopental in 77 adults, respiratory resistance was lower after propofol when compared to either thiopental or etomidate [67]. Pizov et al. randomized a cohort of asthmatic and non-asthmatic patients to anesthetic induction with thiopental/thiamylal, methohexital, or propofol, again at equipotent doses. Following endotracheal intubation, auscultation was performed to evaluate the presence of wheezing [68]. In asthmatic patients, the incidence of wheezing was 45 % with thiopental/thiamylal, 26 % with methohexital, and 0 % with propofol. Propofol's beneficial effects on airway reactivity are further supported by animal studies which show attenuation of carbachol-induced airway constriction in canine tracheal smooth muscle and prevention of reflex bronchoconstriction to several known provocative agents in isolated guinea pig trachea smooth muscle [69, 70]. In both an animal model and a human study, these beneficial effects were present only with the propofol solution that has EDTA as the preservative (Diprivan®) and not the formulation containing sodium metabisulphite [71, 72].

Like the barbiturates and etomidate, propofol decreases the cerebral metabolic rate ($CMRO_2$) leading to reflex cerebral vasoconstriction thereby decreasing CBF, CBV and intracranial pressure (ICP) [73]. Several animal studies have confirmed the potential beneficial effects of propofol on cerebral vascular and metabolic dynamics [74, 75]. However, the beneficial effects can be offset by significant hemodynamic effects. There are conflicting results in regards to the effects of propofol on ICP from studies in humans. Although ICP is decreased in the majority of the studies, propofol's lowering of MAP may result in a decrease of the cerebral perfusion pressure (CPP) with reflex cerebral vasodilation to maintain CBF and a secondary increase of ICP [76–79]. However, if MAP is maintained at baseline with vasoactive agents, propofol may lower ICP and thus increase CPP [80]. As with other agents such as the barbiturates which lower the $CMRO_2$, propofol has a protective effect in various animal models of hypoxia-ischemia injury [81–83].

Various neurological manifestations have been reported with the administration of propofol including opisthotonic posturing, myoclonic movements (especially in children), and movements that may resemble seizure activity [84–86]. Myoclonus, opisthotonic posturing, and other movements with propofol may be due to propofol's antagonism at glycine receptors in the subcortical region. To date, there is no formal evidence linking propofol with seizures. In a study evaluating the effects of propofol and thiopental on the surface electroencephalograms of 20 patients undergoing temporal lobe surgery, there was no difference between the two groups in the rate of discharge or extension of the irritable zone [87]. Propofol remains an effective agent for the termination of refractory status epilepticus and remains in various published algorithms regarding recommendations for its treatment [88, 89].

As propofol is delivered in a lipid emulsion, there may be allergic reactions, pain on injection, elevated triglyceride levels, or hypercapnia with prolonged infusions [90, 91]. A propofol infusion of 2 mg/kg/h provides approximately 0.5 g/kg/day of fat and should be taken into consideration when deciding on parenteral nutrition in the ICU setting. Although it was previously thought that cross-reactivity may occur in patients with allergies to egg, egg products, soy beans, or soy products, the validity of this concern has recently been questioned [92].

Pain with the injection of propofol remains a significant complaint especially when injected into the small veins on the dorsum of the hands or feet. Variable success in decreasing the incidence of pain has been reported with various

maneuvers such as the pre-administration of lidocaine, mixing the lidocaine and propofol in a single solution, mixing the propofol with thiopental, diluting the concentration of the propofol, cooling it prior to bolus administration, or the administration of a small dose of ketamine prior to the administration of the propofol [93–97]. One final issue with present with the lipid component of propofol is its potential to serve as a viable growth media for bacteria with reports of bacteremia and postoperative wound infections linked to extrinsically contaminated propofol [98, 99]. Various preservatives are used in different currently available propofol solutions including disodium EDTA, benzyl alcohol, or sodium metabisulfite. In clinical practice, there may be clinically significant differences in these preparations including differential effects on airway reactivity (see above), the compatibility of various medications with the different preparations, and the potency of each preparation. Although a retrospective analysis of dose requirements during sedation for MRI demonstrated a decreased potency of the sodium metabisulfite propofol solution when compared to the EDTA solution, other investigators noted no difference in the cardiovascular or hypnotic effects of the two solutions using bispectral index monitoring [45, 100]. A theoretical disadvantage of disodium EDTA is the chelation and depletion from the body of essential trace minerals such as zinc. Although there are no formal studies demonstrating this as a problem, concerns related to this issue are outlined in the manufacturer's package insert.

Despite its potential benefits in the ICU setting and its efficacy as an infusion for providing sedation during mechanical ventilation, the routine use of propofol infusions is not recommended and in fact, is considered contraindicated by many authorities because of the potential for propofol infusion syndrome [101–104]. Subsequent to the initial reports and the review of Bray et al., the syndrome has been reported in older patients including a 17 year old adolescent and adults [105–107]. In a guinea pig cardiac myocyte preparation, propofol has been shown to disrupt mitochondrial function [108]. Biochemical analysis of two patients who developed propofol infusion syndrome have demonstrated an increase in intermediaries of fatty acid metabolism (acylcarnitine) suggesting impairment of mitochondrial function and the respiratory chain as the biochemical basis of the syndrome [109, 110]. In specific clinical scenarios, propofol infusions are still a needed therapeutic tool in the treatment of refractory status epilepticus, status asthmaticus, or increased ICP. In such cases, intermittent analysis of acid-base status and creatinine phosphokinase is suggested. If a base deficit is noted with an increasing serum lactate, immediate discontinuation of the propofol is recommended. Additionally, the short term administration of propofol (6–12 h) is still utilized in many centers to transition from other agents such as fentanyl and midazolam to allow for more rapid awakening for extubation of the trachea. Short term propofol infusions may also have a role in the arena of procedural sedation as a means of providing sedation during non-painful invasive procedures such as radiologic imaging. Given its lack of analgesic effects, additional analgesic agents may be required when invasive procedures are performed. Although rare, when such procedures are long, concern has also been expressed regarding the potential development of the propofol infusion syndrome [111].

Ketamine

Ketamine, a synthetic derivative of phencyclidine (PCP), was first used in humans in 1965 by Domino and colleagues [112]. Ketamine is unique among the intravenous anesthetic agents as it has coexistent potent analgesic and amnestic qualities. As patients frequently keep their eyes open and yet are unresponsive to painful stimuli, the term dissociative anesthesia is often used to describe this state of amnesia and analgesia. Ketamine's sedative, analgesic, and amnestic properties are mediated through agonism of opioid receptors and antagonism of NMDA receptors. Ketamine contains a chiral carbon in its structure and the preparation most commonly used in clinical practice is a racemic mixture of the two optical isomers [S(+) and R(−)]. In the United Kingdom and Europe the enantiomer, S(+) ketamine, is available. Although conflicting data are present, some clinical trials have suggested that the S(+) enantiomer provides effective analgesia and sedation while limiting adverse effects including emergence phenomena. Metabolism of ketamine occurs primarily by hepatic N-demethylation to norketamine. The latter compound retains approximately 30–40 % of the analgesic and sedative properties of the parent compound. Higher concentrations of norketamine are produced with oral versus intravenous administration thereby suggesting that norketamine plays a more significant role in the clinical effect with the oral versus the intravenous route. Given its dependence on hepatic metabolism, doses should be adjusted in patients with hepatic dysfunction. Dose adjustments may also be required in patients with significant renal dysfunction since norketamine elimination is dependent on renal clearance. Because ketamine is highly lipophilic its volume of distribution is quite high, and thus with a single bolus dose, it exhibits a relatively rapid redistribution.

Beneficial properties of ketamine include preservation of cardiovascular function and limited depression of respiratory mechanics with maintenance of central control of respiration. These properties make it an effective and popular agent in the arena of procedural sedation during painful, invasive procedures in the spontaneously breathing patient [113]. Ketamine generally increases heart rate and blood pressure as well as provides bronchodilatation due to the release of endogenous catecholamines [114]. Although the indirect

sympathomimetic effects from endogenous catecholamine release generally overshadow ketamine's direct negative inotropic properties, maintaining blood pressure and heart rate, hypotension and even cardiovascular collapse may occur in patients with diminished myocardial contractility or in those with chronic illnesses who have depleted their endogenous catecholamine stores [115, 116].

Given its effects at the opioid and NMDA receptors, there is growing interest in the use of ketamine for the management of acute pain especially during the postoperative period. Following major surgery, when it is co-administered in low doses during morphine analgesia, ketamine reduces postoperative opioid consumption and lowers opioid-related adverse effects [117–120]. As NMDA receptor stimulation may be one factor resulting in the development of tolerance to opioid-induced sedation and analgesia, there is interest in the potential benefits of using a low dose ketamine infusion to delay tolerance during prolonged ICU infusions of sedatives. However, the preliminary clinical data have failed to demonstrate its efficacy in this regard [121].

Ketamine has have minimal effects on various respiratory parameters including functional residual capacity, minute ventilation, and tidal volume [122, 123]. The release of endogenous catecholamines generally results in improved pulmonary compliance, decreased resistance, and prevention of bronchospasm [124]. Despite the fact that minute ventilation is generally maintained, hypercarbia with a rightward shift of the CO_2 response curve may occur [125]. Although generally effective in allowing maintenance of protective airway reflexes and spontaneous ventilation, ketamine can result in loss of protective airway reflexes, gastric aspiration, and apnea especially when co-administered with opioids [126, 127].

Alternative, non intravenous routes of delivery, have been reported with ketamine including oral and transmucosal (nasal, rectal) administration [128–130]. These alternative routes of delivery have been used for one time dosing of the agent for sedation during a procedure or as a premedicant to anesthetic induction. Additionally, ketamine is occasionally administered via the IM route in uncooperative patients without venous access.

The adverse effect of ketamine that tends to attract the most attention is its potential to cause emergence phenomena or hallucinations. Because of these concerns, clinical practice generally includes the co-administration of a benzodiazepine, or GABA agonist of some kind, along with or prior to the administration of ketamine. The single enantiomer form, S(+) ketamine, has been released outside of the United States for clinical use. The initial clinical trials have demonstrated that S(+) ketamine is twice as potent as the racemic formulation and that it may offer the clinical advantages of fewer psychomimetic effects, less salivation, and a shorter recovery time [131].

An issue of potential concern and ongoing controversy regarding ketamine is its effects on pulmonary vascular resistance (PVR) [132–135]. Many of these studies were performed without full respiratory support and changes in $PaCO_2$ may have impacted PVR. More recently, Williams et al. evaluated the effects of ketamine on PVR during sevoflurane anesthesia (0.5 MAC) with controlled ventilation in 15 infants and children with pulmonary hypertension [136]. There were no changes in mean systemic arterial pressure, systemic vascular resistance index, mean pulmonary artery pressure, pulmonary vascular resistance index, cardiac index, and $PaCO_2$. The safety of ketamine in patients with congenital heart disease is further evidenced by experience with its use during spontaneous ventilation for sedation during pediatric cardiac catheterization with less hypotension than propofol [137, 138].

An additional area of controversy surrounds ketamine regarding its effect on intracranial pressure (ICP). These effects may be indirect, secondary to changes in $PaCO_2$ or the result of a direct effect on the cerebral vasculature. Clinical work from the 1970s reported that ketamine increased ICP thereby suggesting that it was contraindicated in patients with altered intracranial compliance [139, 140]. These clinical studies were supported by animal investigations demonstrating that the alterations in ICP resulted from direct cerebral vasodilatation, mediated through central cholinergic receptors [141, 142]. However, more recent data from both animal and human studies have shown no change or even a decrease in ICP following the administration of ketamine [143–148]. In CPP in adult patients anesthetized with isoflurane and nitrous oxide [148].

A final controversial issue related to the CNS effects of ketamine is its use in patients with an underlying seizure disorder. EEG recordings in children and laboratory animals during ketamine administration have demonstrated increased frequency and amplitude of the waveforms of the EEG with occasional paroxysmal seizure activity [149, 150]. However, no clinical evidence of seizure activity has been reported with ketamine administration. Studies in laboratory animals have demonstrated the anticonvulsant effects of ketamine and there is at least one clinical report as well as animal data describing its use for the treatment of refractory status epilepticus [151–153].

Etomidate

Etomidate is an intravenous anesthetic agent that was introduced into clinical practice in 1972. Like the barbiturates and propofol, it exerts its primary effects of sedation and amnesia through the GABA system. Etomidate is the only intravenous anesthetic agent that is supplied clinically as a single enantiomer as only the R(+) form has clinical effects. It is

supplied in a 2 mg/mL with propylene glycol (35 % by volume) as the diluent. The solution has a pH of 6.9 and an osmolality of 4640 mOsm/L. Although not available in the United States, a novel preparation in a lipid formulation (Etomidate-Lipuro®) may limit pain on injection as it does not contain propylene glycol. Following intravenous administration, loss of consciousness is rapid (15–20 s, or one "arm-brain" circulation time). The duration of the clinical effect following a single bolus dose is related to redistribution rather than metabolism and clearance. Etomidate undergoes hepatic metabolism with an elimination half-life varying from 2.9 to 5.3 h [154]. Beneficial CNS effects include a decrease of the $CMRO_2$, CBF, and ICP. Cerebral perfusion pressure (CPP) is maintained because of minimal effects on myocardial function and MAP [155].

Like the barbiturates and propofol, etomidate results in a dose-dependant depressant effect on respiratory function and can result in apnea depending on the dose used, concomitant use of other respiratory depressant medications, and the patient's underlying status [156]. Although both methohexital and etomidate decrease the slope of the CO_2 response curve, the effect has been shown to be more pronounced with methohexital [157]. With methohexital, minute ventilation at an end-tidal CO_2 of 50 mmHg decreased from 14.6 to 4.3l/min while it increased from 17.9 to 31.6 l/min with etomidate ($p<0.05$). The increase in minute ventilation with etomidate resulted from an increase in respiratory rate without a change in tidal volume. Despite this relative sparing of respiratory function, an increased incidence of apnea has been reported following etomidate in patients pretreated with either opioids or benzodiazepines [158, 159].

Etomidate's place as an agent for the induction of anesthesia and for procedural sedation results from its negligible effects on myocardial function and intracerebral dynamics even in patients with significant alterations in myocardial function [160]. Despite its lowering of CBF and ICP, induction or sedative doses of etomidate can produce increased electroencephalogram (EEG) activity and epileptic-like EEG potentials in patients with underlying seizure disorders [161–164]. Myoclonic movements are also a frequently observed following the rapid intravenous administration of etomidate [165]. Although these movements may simulate or appear to be tonic-clonic seizure activity, no epileptiform discharges are noted. It has been suggested that the myoclonic movements are of spinal origin resulting from disinhibition of inhibitory neuronal pathways. Pretreatment with fentanyl, benzodiazepines, or a small dose of etomidate has been shown to be effective in decreasing the incidence of myoclonus. A trial of etomidate for sedation during computerized tomography was discontinued due to an unacceptably high incidence of involuntary motor movements preventing completion of the scan [166].

Although a relatively large clinical experience exists in the adult population, there are limited data regarding the use of etomidate in pediatric-aged patients [167]. Much of the data are anecdotal from case reports or small series demonstrating its safety even in infants and children with depressed myocardial function [168, 169]. Despite the relatively limited clinical data regarding its use in infants and children, recent reviews continue to suggest its safe use as a single bolus dose for critically ill pediatric patients requiring endotracheal intubation [170].

The most significant concern with etomidate and the factor limiting its long-term administration in the ICU setting is its effects on the endogenous production of corticosteroids. This effect was identified when an increased risk of mortality was noted in adult ICU patients who were sedated with a continuous infusion of etomidate [171]. Etomidate inhibits the enzyme 11-β hydroxylase which is necessary for the production of cortisol, aldosterone, and corticosterone. At present, significant controversy surrounds the clinical significance of the adrenal suppression following a single induction dose of etomidate with some authors calling for the abandonment or at least a re-evaluation of the use of etomidate [172–174]. The duration of the adrenal suppression produced by a single induction dose of etomidate has varied from study to study with some reports demonstrating suppression for days after a single induction dose [175–178]. In a cohort of 40 critically ill adult patients, the incidence of adrenal insufficiency, defined as a failure of the serum cortisol level to increase by 9 μg/dL after a 250 μg ACTH stimulation test, following a single dose of etomidate was 80 % at 12 h, 9 % at 48 h, and 7 % at 72 h [178]. Despite these findings, no difference in outcome was reported while other studies have demonstrated an improved clinical course with decreased vasopressor therapy when etomidate was used for sedation during endotracheal intubation [179]. Perhaps the most compelling data against the use of etomidate, at least in patients with possible sepsis, comes from the CORTICUS trial [180]. Although the trail was not powered for outcomes analysis, a *post hoc* analysis revealed that patients who had received etomidate had a significantly higher mortality rate. Clinical practice guidelines for the treatment of septic shock in pediatric and neonatal patients from the American College of Critical Care Medicine state that: "Etomidate is popular as an induction agent because it maintains cardiovascular stability through blockade of the vascular K + channel; however, even one dose used for intubation is independently associated with increased mortality in both children and adults with septic shock, possibly secondary to inhibition of adrenal corticosteroid biosynthesis. Therefore, it is not recommended for this purpose." Only one member of the task force supported the use of etomidate in pediatric septic shock with the caveat that stress dose hydrocortisone be administered" [181]. Despite

these concerns, etomidate has yet to be abandoned in critically ill patients and may still play a role as an effective agent to provide sedation and amnesia during endotracheal intubation in critically ill pediatric patients given its beneficial effects on CNS dynamics and myocardial function [182]. The lack of cardiovascular effects with etomidate makes it particularly valuable in patients who may not tolerate a decrease in systemic vascular resistance or myocardial contractility. Given its effects on cerebral dynamics, it also should be considered for patients with increased ICP with or without associated myocardial dysfunction. However, until further data are available, its use in patients with potential sepsis is not recommended.

Benzodiazepines

Since the synthesis of diazepam in 1959, multiple different benzodiazepines have been synthesized. Various investigators have pursued more potent and more water-soluble forms that achieve similar results. In 1976, these initiatives yielded midazolam, the first water-soluble benzodiazepine to be used in clinical practice. These agents produce amnesia, anxiolysis, and sedation through their effects on the inhibitory neurotransmitter, γ-amino butyric acid (GABA). Benzodiazepines bind to the α-subunit of the GABA receptor thereby facilitating binding of the GABA molecule to the β-subunit. Benzodiazepines in common clinical use in the United States for sedation in the PICU include midazolam and lorazepam. Diazepam was formerly a commonly used agent for sedation in both the pediatric and adult intensive care units as its high lipid solubility results in a rapid onset of action, but its low water solubility requires administration in a solution of propylene glycol. Diazepam is also commercially available in a lipid formulation which alleviates the discomfort with the intravenous administration of the propylene glycol preparation [183, 184]. Diazepam has fallen out of favor as an agent for sedation in the PICU setting because of its prolonged duration of action related to its metabolism to active compounds including oxazepam and N-desmethyldiazepam. These active metabolites have elimination half-lives that far exceed the parent compound.

Midazolam is an imidazole-benzodiazepine with a rapid onset of action and a short elimination half-life [185]. Given its rapid onset and water solubility with limited pain on injection, midazolam has found a role for both procedural sedation when administered by intermittent bolus dosing as well as for sedation during mechanical ventilation when used as a continuous infusion except for brief procedures. Clinical experience and years of its use have demonstrated the efficacy of continuous midazolam infusions for sedation in the PICU patient in doses ranging from 0.05 to 0.2 mg/kg/h [186–189]. The availability of midazolam in generic form makes it a cost effective form of sedation in both the PICU setting and arena of procedural sedation.

Although typically administered intravenously in the PICU patient, midazolam remains unique among other agents used in the PICU setting in that alternative, non-intravenous routes of delivery have been used clinically including oral, rectal, transmucosal (nasal, rectal) and subcutaneous administration [190–193]. The oral, rectal, and transmucosal routes are generally used as a route for its administration as a premedicant prior to anesthetic induction in patients without intravenous access while subcutaneous administration has been used with a slow weaning protocol to prevent withdrawal followed prolonged administration [194]. Except for subcutaneous administration, increased doses are required when dosed via alternate routes due to decreased bioavailability.

In many centers, oral midazolam is currently the preferred agent as a premedicant in the operating room with doses ranging from 0.25 up to 0.7 mg/kg. The primary disadvantage of oral administration is a bitter taste when the IV preparation (5 mg/ml) is used which contains the preservative, benzyl alcohol. Because the taste is frequently masked by mixing the drug with flavored solutions or other medications, concern has been raised regarding the potential for the alteration of the absorption characteristics of midazolam. Midazolam normally exists with its two structures, an open and closed ring, in equilibrium. The latter is lipophilic and therefore is physiologically active. The proportion of each ring form in solution is pH dependent. With a lower pH, there is more of the open ring configuration. A commercially available preparation of midazolam in a cherry-flavored solution for oral administration is available. Because of the controlled pH during manufacturing, the preparation results in effective sedation with lower doses compared to use of the IV preparation [195]. Additional non-parenteral administration routes include intranasal and sublingual administration with doses ranging between 0.2 and 0.4 mg/kg. Onset tends to be more rapid when compared to the oral route although the patient may experience a burning sensation as the preservative, benzyl alcohol, may irritate the nasal mucosa.

Midazolam is metabolized by the hepatic P_{450} enzyme system to the major hydroxylated metabolite, 1-OH midazolam. 1-OH midazolam (hydroxymidazolam) has a potency of approximately 20–30 % of the parent compound and is excreted renally. Midazolam undergoes further hepatic metabolism via the glucuronyl transferase system to 1-OH midazolam-glucuronide which is dependent on renal excretion. In the presence of renal insufficiency, 1-OH midazolam-glucuronide accumulates potentiating the effects of midazolam [196]. Several factors which include age and underlying illness may also alter midazolam

pharmacokinetics. Because metabolism is dependent on the hepatic P_{450} system, clearance changes from infancy to adult age and with alterations in hepatic function [197, 198]. The critically ill may represent another population where there is prolonged clearance of midazolam [199, 200].

Lorazepam is another water soluble benzodiazepine metabolized by glucuronyl transferase with pharmacologically inactive metabolites. Medications known to alter the P_{450} system do not alter lorazepam's pharmacokinetics. In advanced liver disease, phase II reactions (glucuronyl transferase) are better preserved than phase I reactions (P_{450} system), thus the pharmacokinetics of lorazepam remain unchanged. Although the Society of Critical Care Medicine guidelines for sedation of adult patients in the ICU setting has recommended lorazepam as the preferred sedative [201], there are fewer reports regarding the use of lorazepam for sedation in the both the pediatric and adult ICU population [202, 203]. Enteral lorazepam has been used to decrease intravenous midazolam requirements during mechanical ventilation in infants and children with a significant reduction in midazolam requirements on the first day and a discontinue of the midazolam infusion in 80 % of the patients by day 3 [204]. Enteral lorazepam has also been successfully used treating and preventing withdrawal following prolonged administration of intravenous benzodiazepines during mechanical ventilation in the PICU population [205].

Intravenous lorazepam solution contains propylene glycol. With prolonged or high-dose intravenous administration issues may arise related to propylene glycol [206–208]. Propylene glycol toxicity presents as a metabolic (lactic) acidosis, renal failure or insufficiency, mental status changes, hemolysis, and an elevated osmolar gap. Propylene glycol is metabolized in the liver to lactic acid and pyruvic acid, which accounts for some of the lactic acidosis. Propylene glycol is also excreted unchanged in the urine making toxicity more likely in the presence of renal insufficiency. Periodic calculation of the osmolar gap (measured osmolarity minus calculated serum osmolarity) may be indicated during high dose or prolonged lorazepam infusions. An increasing osmolar gap has been shown to be predictive of increasing serum propylene glycol levels [208]. The osmolar gap is used as a surrogate for actual plasma propylene glycol concentrations although this can be measured by reference laboratories. As neonates and especially preterm infants are unable to handle propylene glycol due to hepatic and renal immaturity, continuous infusions of lorazepam are not recommended in this population.

Conclusion

In the operating room, the intensive care unit, and the arena of procedural sedation, various agents are used to provide sedation and analgesia. Depending on the type of procedure, varying depths of sedation through general anesthesia may be required. The agents used for the induction and maintenance of sedation and general anesthesia are broadly classified into either inhalational (volatile) or intravenous agents. The choice of the class of agent and the specific drug is broadly based on the patient's physical status and underlying co-morbid conditions, and the clinical scenario. Recent advances in pharmacology and new pharmacokinetic data with older agents continues to provide use with a greater choice of agents and a better understanding of how to use these agents in our practice. In addition to their use in the operating room for the provision of general anesthesia, many of these agents are used outside of the operating for either their sedative properties or even occasionally for their therapeutic effects. Examples of this include propofol for procedural sedation, pentobarbital to control intracranial pressure (ICP) or isoflurane for the treatment of status asthmaticus. Despite the relative safety of these agents, they all should be used only with appropriate monitoring of the patient's physiologic status and attention to guidelines for procedural sedation from various licensing boards and organizations. We must also recognize lesions learned from drugs like halothane, etomidate and propofol. Ongoing vigilance is necessary to identify previously unrecognized adverse effects. With these caveats in mind, these agents can provide the much needed sedation and anxiolysis in the critically ill pediatric patient.

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Sedation and Analgesia

3

Eric Lloyd, Manal Alasnag, and Joseph D. Tobias

Abstract

Various factors may be responsible for pain and anxiety in Pediatric Intensive Care Unit (PICU). As such, there may be a need for analgesia and sedation during the course of therapy. Pain may result from the presence of an endotracheal tube and ongoing mechanical ventilation, an underlying medical illness, a surgical procedure, trauma, or the various invasive procedures that are required as part of the daily care in the PICU. Although non-pharmacologic measures including age-appropriate communication, reassurance, parental presence, and psychological interventions may decrease the impact of these factors, pharmacologic intervention is frequently necessary. The following chapter reviews the key decision points when providing sedation and analgesia in the PICU including choice of medication as well as the route and mode of administration. Although benzodiazepines and opioids remain the primary agents used, specific scenarios may require alternative choices. Agents discussed include the inhalational anesthetic agents, benzodiazepines, etomidate, ketamine, propofol barbiturates, opioids, phenothiazines and butyrophenones, α_2-adrenergic agonists (dexmedetomidine), and chloral hydrate. Regardless the agent chosen, given the frequent presence of co-morbid conditions, adverse effects on physiologic function may occur with the use of sedative and analgesic agents.

Keywords

Sedation • Analgesia • Inhalational anesthetic agents • Benzodiazepines • Etomidate • Ketamine • Propofol barbiturates • Opioids • Phenothiazines and butyrophenones • Dexmedetomidine • Chloral hydrate

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Introduction

Admission to and the subsequent care required in the Pediatric Intensive Care Unit (PICU) can be a frightening and painful experience to infants and children of all ages. Pain and its deleterious physiologic effects may be the result of an underlying medical illness, a surgical procedure, trauma, or the various invasive procedures that are required as part of the daily care in the PICU. These invasive procedures may include burn dressing changes, the placement of intravascular catheters, or the mere presence of an endotracheal tube (ETT) for mechanical ventilation. The latter continues to represent the most frequent need for sedation and analgesia during the PICU course. The pain caused by an

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ETT for the provision of mechanical ventilation can be significant in that it has been shown that 26.3 % of adults remembered mechanical ventilation and approximately 25 % would have chosen not to receive mechanical ventilation had it been any more painful [1]. In addition to physical pain, emotional pain can result from separation from parents and loved ones, disruption of the day-night cycle, unfamiliar people, the incessant noise of machines and monitoring devices that are present in the PICU, fear of death, and loss of self-control. Although non-pharmacologic measures including age-appropriate communication, reassurance, parental presence, and psychological interventions may decrease the impact of these factors, pharmacologic intervention is frequently necessary.

Prior to instituting pharmacologic control of pain or anxiety, a thorough evaluation of the patient and preparation of the environment is necessary (Table 3.1). Such preparation and the institution of ongoing monitoring of the patient's physiologic function is paramount in minimizing the potential adverse physiologic effects which may occur when sedative or analgesic agents are administered. This preparation ensures that the appropriate equipment and personnel are available to immediately intervene if such adverse effects occur. Additionally, before sedation and analgesia are provided or escalated, treatable and potentially life-threatening causes of agitation must be identified. These may include hypoxemia, hypercarbia, cerebral hypoperfusion, necrotic bowel, or compartment syndrome. Any time that sedation and analgesic agents are administered, adverse effects on physiologic functions may occur. Given such issues, specific guidelines for the preparation and monitoring of patients during the provision of sedation have been published by national organizations including the American Academy of Pediatrics and the American Society of Anesthesiologists [2–4]. Although the PICU provides the optimal environment for the monitoring of a patient's physiologic function, ongoing monitoring should be continued when patients are transported out of the PICU for various diagnostic or therapeutic procedures. The potential impact of inadequate monitoring on morbidity and mortality during sedation has been clearly demonstrated [5, 6].

To date, there is a limited amount of evidence-based medicine available to provide information for the development of guidelines for the use of sedative and analgesic agents in the PICU setting. Although generally extensively studied in the adult population, many of the pharmacologic agents used in the PICU setting have not been adequately evaluated in children, with limited information regarding the pharmacokinetic and pharmacodynamic properties of analgesic and sedative drugs in critically ill infants and children [7–10]. Pharmacokinetic studies are generally performed in healthy adult volunteers or postoperative patients and then extrapolated to the critical care population. There is likely to be significant differences in end-organ function, cardiorespiratory stability, volume of distribution, and metabolic processes in the PICU patient. Alterations in the pharmacodynamics may also result from drug-drug interactions, end-organ (hepatic, renal) failure or dysfunction, malnutrition, and low plasma proteins with altered drug binding. This may be further complicated by alterations in uptake of the medication if non-intravenous routes are used, variations in drug distribution (due to changes in cardiac output), and differences in the volume of distribution. Pharmacogenetic factors may also affect responses to medications. There are genetic differences that affect the response to and the metabolism of the sedative and analgesic agents. These pharmacogenetic effects extend far beyond simple changes in drug metabolism to receptor function and central processes affecting sedation and analgesia [11]. As we have limited means of identifying the impact of factors on the pharmacokinetics and pharmacodynamics of the medications that are used for sedation and analgesia in the PICU setting, the effects of these agents should be continuously evaluated and changes made to titrate the dose based on the patient's response [12].

Therefore, it is not feasible to approach the provision of sedation and analgesia in the PICU patient using a "cookbook" approach with specific guidelines concerning the medications to be used and their doses. Although starting doses may be based on empiric guidelines and initiated based

Table 3.1 Preparation for sedation in the Pediatric ICU patient

1. Rule out treatable causes of agitation: Hypoxia Hypercarbia Cerebral hypoperfusion Bladder distention Necrotic bowel Compartment syndrome
2. Identify the etiology of the distress to guide the choice of the agent or agents as well as the need to provide sedation, anxiolysis, amnesia, analgesia or some combination of the above
3. Monitor patient in accordance with the standards outlined by the American Academy of Pediatrics for procedural sedation and analgesia
4. Titrate the initial bolus dose of the medication and subsequent infusion rates based on the patient's clinical response
5. Use formalized sedation and pain scales or scoring systems
6. Observe for adverse physiologic effects. In particular, changes in respiratory or hemodynamic function
7. Monitor the patient for the development of physical tolerance which may necessitate increasing the dose or switching to another agent that acts through a different receptor system
8. When the need for sedation or analgesia is over, identify at risk patients for withdrawal and treat appropriately to prevent withdrawal. Monitor the patient for withdrawal using standardized scoring systems

on the patient's weight, sedative and analgesic agents should be titrated up and down according to the patient's needs and the desired level of sedation. The dosing recommendations provided in this chapter for the specific medications discussed are intended as guidelines for starting doses. In many centers, this incremental increase or decrease in the amount of medication administered is now based on the use of formal sedation scores which are assigned along with the nurse's assessment of the patient's vital signs (see below for a discussion of the assessment of the depth of sedation). The use of such parameters may provide a more effective means of titrating the level of sedation than the adjustment of dosing without formal sedation assessment [13].

Agent, Route, and Mode of Administration

There remains three primary decision points for sedation and analgesia in the PICU patient including: (1) the agent, (2) the route of administration, and (3) the mode of administration. Identifying the cause or anticipated cause of the distress can be used to guide the selection of the agent. Tissue injury or the presence of pain requires the use of agents with analgesic effects while emotional distress and anxiety may be more appropriately treated with agents that possess sedative or anxiolytic properties. As there are a limited number of agents that possess both sedative and analgesic effects, a combination of sedative and analgesic agents may be used. Another factor to consider when choosing the agent is the length of time during which sedation or analgesia is required. This may be extremely variable involving less than 5 min for an invasive procedure, 1–2 h during an MRI scan, or days to weeks in a patient requiring prolonged mechanical ventilation or extracorporeal support.

The second decision point regarding sedative and analgesics is the route of administration. Although the intravenous route is used in most clinical scenarios, alternative, non-intravenous routes may become necessary in specific circumstances. In the PICU setting, there is expanding knowledge regarding the use of alternative routes of delivery (inhalational anesthesia or subcutaneous administration). The subcutaneous or inhalational route may be chosen as the primary route or used as an alternative when drug incompatibilities preclude intravenous administration or in patients with limited intravenous access. However, alternative routes of delivery are not available for all medications (Table 3.2). Chloral hydrate may be administered by the oral or rectal route, isoflurane requires inhalation administration, while propofol can only be administered by the intravenous route. Midazolam and ketamine offer the greatest variety of route of administration with reports of intravenous, intramuscular, subcutaneous, oral, nasal, and sublingual administration.

Table 3.2 Routes of delivery for sedative-analgesic agents

Intravenous
Intramuscular
Subcutaneous
Oral
Transmucosal:
Buccal
Nasal
Rectal
Sublingual
Transdermal
Inhalation

Table 3.3 Agents for pediatric ICU sedation and analgesia

Inhalational anesthetic agents
Benzodiazepines
Opioids
Phenothiazines
Butyrophenones
Anti-histamines
Chloral hydrate
Etomidate
Ketamine
Barbiturates
Propofol
Alpha$_2$ adrenergic agonists

The third of the three primary decision points is the mode of administration which includes continuous administration, intermittent dosing, or patient-controlled techniques. When there is an ongoing need for sedation such as the patient requiring mechanical ventilation, longer acting agents (lorazepam, pentobarbital, morphine) may be used by intermittent, bolus administration and still provide an effective baseline level of sedation. Short-acting agents (midazolam, fentanyl) are generally best administered by a continuous infusion to maintain a steady state serum concentration. An alternative mode, used most commonly in the treatment of acute pain is a patient activated device otherwise known as patient-controlled analgesia (PCA).

The agents available for sedation are listed in Table 3.3. In the course of this chapter, a brief discussion will be provided of each agent, its potential advantage and disadvantages, and reports of its use in the PICU setting. As no single agent will be effective in every patient, basic knowledge regarding the various agents will allow the healthcare provider to switch from one agent to another when the first line drug is either ineffective or associated with adverse effects which requires its discontinuation. Before embarking on the discussion of the agents available and their uses, a review of the methods available to judge the depth of sedation will be provided.

Assessing the Depth of Sedation

During the use of sedative and analgesic agents, the repeated evaluation of the depth of sedation should be incorporated into the PICU routine. Titration of doses can then be individualized, based on the patient's response. Given the significant variability between patients regarding the amount of sedative agents required, this practice allows an ongoing assessment of the patient and adjustment of the infusion rates based on their responses. Over the past few years, there has been a gradual move from the use of subjective measures and assessments made by physicians to the use of formal pain or sedation scoring systems. These are monitored at regular intervals by the nursing staff along with the recording of physiologic vital signs. In many centers, an assessment of pain and sedation is considered the fifth vital sign.

Given its relative novelty to the PICU setting, there is no gold standard for assessing the depth of sedation. The ideal tool needs to be simple to perform as well as easy to repeat and interpret with clear definitions for over and undersedation. Many tools are adapted from intraoperative anesthetic care and therefore put significant emphasis on changes in hemodynamic variables. In children, significant swings in physiologic response may be caused by subtle stimuli such as separation anxiety, the underlying disease pathology and the various pharmacological agents that are administered. This makes monitoring and assessing sedation in the PICU a particularly challenging task.

The most commonly used PICU sedation scores evaluate physiologic variables, an objective assessment of the patient's depth of sedation, or a combination of the two. One commonly used scale, the COMFORT score, combines a patient's response or movement with physiologic parameters [14]. The score includes the measurement of alertness, respiration, blood pressure, muscle tone, agitation, movement, heart rate, and facial tension. This scoring system has been designed to measure stress in the critically ill requiring mechanical ventilation. It has been validated in the pediatric-aged patient and may have utility in providing cutoff scores for implementation in guidelines [14–16]. The COMFORT score cannot be used if patients are receiving neuromuscular blockade and some have criticized it for being too laborious to calculate [17]. Because of these concerns, Ista et al. have attempted to address these concerns by modifying the original COMFORT score [18]. The investigators coined the phrase "COMFORT-B score", eliminated the physiologic variables, and provided new cutoff points for the diagnosis of oversedation or undersedation.

Other scoring systems to assess the ICU patient have also eliminated the use of physiologic parameters. Many of these scales were developed in adult ICU's, but have also been used in the PICU patient. The Ramsay sedation scale originally categorized the patient's conscious level into six levels. This has been subsequently modified to eight levels. Level 1 identifies patients who are awake, anxious and agitated; while level 8 identifies a deep sedation state in which the patient is unresponsive to stimuli including painful ones. The main disadvantage of using this tool in the PICU setting is that it is a test of arousability. Values are assigned based on simple observation of the patient in addition to auditory and tactile stimuli. One of the concerns of the Ramsay scale is that in differentiating the deeper levels of sedation, a tactile stimulus (glabellar tap) is used, therefore disturbing an otherwise comfortable and resting patient. Though simple to perform, the Ramsay sedation scale has not been validated in children and cannot be used in deeply sedated or paralyzed patients. It has been suggested as a useful tool in monitoring during procedural sedation [19, 20]. The Sedation-Agitation Scale also eliminates the physiologic parameters and visually assesses the level of the patient's comfort, grading it from 1 (unarousable) to 7 (dangerous agitation such as pulling at the ETT) [21]. The Hartwig score also uses a visual assessment of the patient, but includes a response to tracheal suctioning thereby eliminating its use in non-intubated patients [22].

Scales that assess the response to a tactile stimulus require disturbing the patient to differentiate between the deeper levels of sedation while the Hartwig scale incorporates a noxious stimulus that is part of the PICU routine in intubated patients, tracheal suctioning. The major drawback of scales that evaluate a patient's response to a stimulus or observe their behavior is that they are not applicable during the use of neuromuscular blocking agents. In order to avoid subjective assessment, tactile stimulation and enable the assessment of pharmacologically paralyzed patients, monitors have been developed to evaluate the depth of sedation based on the analysis of the electroencephalogram (EEG).

Although, there are now several of these "depth of anesthesia" monitors available, the one that has seen the greatest use both in and out of the operating room is the first one introduced into clinical practice, the Bispectral Index (BIS monitor, Aspect Medical, Newton, MA). The BIS monitor uses a programmed algorithm to evaluate and interrogate the processed EEG pattern. It provides a numeric value ranging from 0 (isoelectric) to 100 (awake with eyes open). Its predominant clinical use has been intraoperatively to monitor the effects of general anesthetic and sedative agents and provide a measure of the depth of anesthesia or sedation. Although a BIS value less than 60–70 has been shown to correlate with a low probability of intraoperative awareness, its superiority over other intraoperative monitors such as end-tidal gas monitor as a means of limiting awareness has not been proven [23–26].

The BIS monitor has also been used in settings outside of the operating room including the PICU, where assessment of sedation is critical to interventions such as mechanical

ventilation or invasive procedures [27–30]. Although the results have been mixed [16, 17], the majority of reports have demonstrated a clinically acceptable correlation between the BIS monitor and commonly used PICU sedation scores such as the COMFORT score [29, 31, 32]. Although these monitors may not be necessary for the majority of patients receiving mechanical ventilation; in scenarios where clinical sedation scales are not applicable such as the patient who is receiving pharmacologic paralysis, these devices may have clinical utility. Without titrating sedation using such monitors, it has been shown that children who are receiving neuromuscular blocking agents may be excessively sedated [33]. Although there are limited data to show the opposite is a problem, pharmacologic paralysis without adequate sedation and amnesia must be recognized and appropriately corrected. An additional advantage of the depth of anesthesia monitor is that it provides a continuous numeric readout using a simple 0–100 scale that is immediately available at the bedside as opposed to sedation scoring systems that provide only an intermittent assessment and require time to assess and add various parameters.

BIS monitoring has also been used in the arena of procedural sedation [32–35]. These studies have demonstrated a good correlation with clinical scales such as the Ramsay Scale and the University of Michigan scale during the use of sedation for invasive procedures in children [33, 34]. Powers et al. used the BIS to titrate levels of propofol to a BIS of 50 in order to maintain an adequate sedation for painful procedures [36]. Motas et al. demonstrated that the depth of sedation as judged by the BIS monitor was predictive of adverse airway events during the administration of procedural sedation by non-anesthesiologists [37]. Episodes of oxygen desaturation and airway events respectively increased from (1 and 0) of 20 patients when the BIS number was 71–90 to (2 and 3) of 17 patients when the BIS number was 61–70 to (4 and 4) of 24 patients when the BIS number was less than 60.

However, there are limitations to the use of BIS monitoring in the PICU setting. Although various studies in both adult and pediatric ICU populations have demonstrated a clinically useful correlation between the BIS number and various sedation scales, these same studies reveal that there is a wide variation of BIS numbers for any specific sedation scale. Part of this variation may be related to interference from electromyographic (EMG) artifact from facial musculature which falsely elevates the BIS number [38, 39]. In fact, one group of investigators demonstrated that the BIS number decreases following the administration of neuromuscular blocking agents in fully awake volunteers thereby demonstrating the EMG interference [39]. The newer version of the BIS probes now incorporates a sensor that is meant to eliminate EMG interference from the BIS algorithm and may address this issue. Natural sleep phases also confound the interpretation of the BIS value as the phases of deep sleep in a sedated patient may be identified as over-sedation. It was also noted although BIS values may accurately predict transition between light and moderate sedation, they are poor predictors of the transition between moderate and deep sedation [40]. The BIS monitor and its EEG algorithm was originally developed for use with inhalational anesthetic agents and not the myriad of sedative and analgesics used for ICU sedation. Therefore, its correlation with depth of sedation/awareness is not as accurate with medications other than the inhalational anesthetic agents, barbiturates, benzodiazepines, and propofol. Brown-McDermott et al. demonstrated that the BIS correlated with the University of Michigan Sedation Score when pentobarbital or benzodiazepines were used for sedation, but not when the regimen included chloral hydrate, meperidine, hydroxyzine, or ketamine [32]. Other studies have demonstrated the inaccuracy of the BIS monitor with the administration of etomidate or agents such as xenon or nitrous oxide which act through the N-methyl-D-aspartate (NMDA) system [27–29, 41–43].

Measurement of middle latency auditory evoked potentials (MLAEPs) is a tool that records changes in cerebral auditory waves through electrodes placed on the skin of the scalp. An auditory stimulus is applied through headphones and monitors display a numerical index which correlates with the level of sedation. This method has not been validated in children and the use of scalp electrodes and constant auditory stimulation has limited its use for continuous monitoring [44]. Despite these shortcomings, awareness monitoring is seeing increased use in the PICU setting and may offer specific advantages over the use of sedation scales or rather be an effective adjunct that is combined with routine sedation scoring.

Agents for Sedation and Analgesia

Inhalational Anesthetic Agents

The inhalational or volatile anesthetic agents can be grouped into one of three basic chemical structures: alkanes (halothane), methyl-ethyl ethers (isoflurane, desflurane, and enflurane) or methyl-isopropyl ethers (sevoflurane). Although previously in common clinical use for the induction and maintenance of anesthesia, halothane has largely been replaced by sevoflurane. Halothane was removed from the US market because of its negative inotropic and chronotrophic and its association with perioperative cardiac arrest in infants and children.

The intraoperative use of the volatile anesthetic agents has demonstrated several characteristics which may make them useful agents for PICU sedation. These include a rapid onset, rapid awakening upon discontinuation, and ease of

control of the depth of sedation. As these agents are volatile substances, they are easily vaporized and administered by the inhalational route. The inhalational anesthetic agents also provide the therapeutic effects of bronchodilatation, myocardial preconditioning, and cerebral protection.

The volatile anesthetic agents (halothane, enflurane, isoflurane, sevoflurane and most recently desflurane) have all been used for ICU sedation, with isoflurane being the most commonly used agent [45–48]. Despite the fact that these agents are all grouped in the category of inhalational or volatile anesthetic agents, their physiologic effects on end-organ function are distinctly different. As noted above, halothane is no longer in common clinical use because of its deleterious physiologic effects on myocardial performance. Additional issues include a pro-arrhythmogenic effect especially in the setting of increased catecholamines, hypercarbia or when used in conjunction with other medications (e.g., aminophylline) and the development of hepatitis related to an immunologic reaction directed against the oxidative metabolite, trifluoroacetic acid [49, 50]. Although hepatitis may occur with the other volatile agents, the incidence is less due to their limited metabolism (only 0.2 % with isoflurane) compared with that of halothane (15–20 %).

Adverse effects with the prolonged administration of enflurane, including a similar negative inotropic effect and the release of fluoride during metabolism, limit its use in the ICU and also in the operating room. Although only 2 % of enflurane undergoes metabolic degradation, the carbon atoms of its methyl and ethyl groups are highly substituted with fluoride. Therefore, serum fluoride concentrations are elevated following prolonged administration. End-organ effects on renal function of elevated plasma fluoride concentrations in excess of 50 μmol/L include a decreased glomerular filtration rate and renal tubular resistance to vasopressin with nephrogenic diabetes insipidus.

Three to five percent of sevoflurane also undergoes metabolism and like enflurane, sevoflurane is highly substituted with fluoride. Although its prolonged administration can also result in elevated serum fluoride concentrations, there is no evidence to suggest that these have deleterious effects on renal function. When comparing sevoflurane to propofol for the sedation of adult patients after coronary bypass surgery, sevoflurane proved to be safe and also led to shorter times of mechanical ventilation, ICU stay, and hospital stay [51]. Similarly, Mesnil et al. noted no adverse effect on renal or hepatic function with the use of sevoflurane for sedation and also noted significantly shorter wake-up times and less extubation delay when compared to propofol and midazolam for 47 intubated adult patients requiring sedation for mechanical ventilation over a period of 24–96 h [52].

Desflurane is the newest of the inhalational anesthetic agents. Its beneficial properties include low blood:gas and blood:fat solubility coefficients, thereby resulting in a rapid onset and rapid awakening upon its discontinuation. Meiser et al. compared propofol with desflurane for postoperative sedation of adult patients during mechanical ventilation [53]. Using the BIS monitor to adjust medication administration, the patients were sedated for a period of time ranging from 3 to 22 h. Patients sedation with desflurane had shorter and more predictable emergence times and a faster return of mental recovery when compared to propofol. Despite the successes of desflurane; until additional experience has been reported, one must be cognizant of the potential adverse effects that have been reported with desflurane during its extensive intraoperative use. These adverse effects include hypotension primarily from peripheral vasodilatation, rebound tachycardia from stimulation of the sympathetic nervous system, and direct irritant effects on the airway thereby making it less than optimal in patients with airway hyperreactivity.

Additional concerns with all of the inhalational anesthetic agents include their potential as a trigger agent for malignant hyperthermia, cost issues, effects on intracranial pressure (ICP), and alterations of the metabolism of other medications. As non-specific vasodilators, these agents cause cerebral vasodilatation resulting in an increase in cerebral blood volume and ICP in patients with compromised intracranial compliance. Cerebral vasodilatation is least with isoflurane or desflurane and can be blunted by hypocarbia [54, 55]. The inhalational anesthetic agents alter the metabolism of several medications which may be administered in the PICU setting including lidocaine, β-adrenergic antagonists, benzodiazepines, and local anesthetic agents [56].

Given the potential problems with the other agents and the fact that the majority of the clinical experience has included isoflurane for ICU sedation, it remains the agent chosen most commonly for prolonged sedation in the ICU setting. Isoflurane's primary hemodynamic effects include peripheral vasodilatation and a decrease in afterload with an increase in cardiac output. Peripheral vasodilatation may be accompanied by a reflex tachycardia that can increase myocardial oxygen demand. Thus, isoflurane should be used cautiously in patients at risk for myocardial ischemia or in those who are unable to tolerate tachycardia and a decrease in afterload.

Reports of the use of the volatile agents in PICU patients remain anecdotal. In the majority of cases outlining the administration of these agents in the PICU, they were used for the therapeutic effects to treat bronchospasm more than to provide sedation. One of the largest reports to date outlines the use of isoflurane for sedation during mechanical ventilation in ten patients, ranging in age from 3 weeks to 19 years [57]. Effective sedation was achieved in all patients without adverse effects on end-organ function. The plasma fluoride concentration correlated with the duration of isoflurane administration. The highest fluoride concentration

was 26.1 μmol/L without evidence of renal toxicity. After discontinuation of isoflurane, five patients developed non-purposeful movements and agitation suggestive of withdrawal. These five patients had received more than 70 MAC-hours of isoflurane.

Despite the reports of the successful use of the volatile agents in the ICU setting, the major barrier to the application of these techniques is the logistic problem of delivering the inhalational anesthetic agents outside of the operating room. As they are classified as general anesthetic agents, local and state regulations may restrict who can adjust the inspired concentration. Changes in the inspired concentration may need to be made by physicians or even members of the anesthesiology staff and not the nursing staff, thereby increasing the manpower issues of this type of sedation. When administered in the operating room, the exhaled gases from the ventilator and anesthesia machine are collected (scavenged) and vented out of the operating room. Since ICU ventilators do not routinely scavenge exhaled gases, effective scavenging or absorption devices (activated charcoal) must be connected to ICU ventilators to prevent environmental pollution. Additional equipment that is required includes a vaporizer and an infra-red monitor to measure the end-tidal concentration of the drug.

The Anesthetic Conserving Device (AnaConDa, Hudson RCI, Upplands Vasby, Sweden) has been developed in an attempt to facilitate the administration of the volatile agents outside of the operating room. This device attaches in-line between the Y-piece of the ventilator and the 15 mm adaptor at the end of the endotracheal tube. A syringe pump delivers the anesthetic agent to a membrane in the device that allows vaporization of the anesthetic agent as the gas from the ventilator flows over it. Sackey et al. compared the effects of isoflurane sedation using the Anesthetic Conserving Device with intravenous midazolam in a cohort of 40 adult ICU patients [57]. The percentage of time within the desired range of sedation was similar between the two groups (54 % with midazolam versus 59 % with isoflurane). Extubation times (10 ± 8 versus 252 ± 271 min) and the time to follow verbal commands (10 ± 8 versus 110 ± 132 min) were shorter with isoflurane than with midazolam. The authors concluded that the Anesthetic Conserving Device allowed easy titration and administration of isoflurane without costly equipment and could be safely managed by the nursing staff. However, this device does not eliminate the need to scavenge the exhaled gases or monitor the end-tidal concentration of the anesthetic agent. To date, experience with this device in the pediatric population is anecdotal [58, 59]. Although preliminary success was reported, given the dead-space of the device, significant rebreathing may occur in patients who weigh less than 20–30 kg. As such, the device must be placed in the inspiratory limb in smaller pediatric patients.

Benzodiazepines

The benzodiazepines remain the most commonly used agent for sedation in the PICU setting. These agents modulate their effects through the inhibitory neurotransmitter, γ-amino butyric acid (GABA). Binding to the α-subunit of the GABA receptor facilitates the interaction of the GABA molecule with the β-subunit of the receptor. This results in increase chloride conduction across the neuronal membrane and neuronal hyperpolarization. The benzodiazepines provide amnesia, sedation, and anxiolysis, but have no intrinsic analgesic properties.

Diazepam was formerly a commonly used agent for sedation in both pediatric and adult ICU's. Its high lipid solubility results in a rapid onset of action; however, its low water solubility requires administration in a solution of propylene glycol, which can cause pain and thrombophlebitis with peripheral administration. A newer formulation of diazepam includes a lipid formulation that has been shown to alleviate the discomfort associated with the intravenous administration of the propylene glycol preparation [60, 61]. However, diazepam use for sedation in the PICU setting is limited by its metabolism to active metabolites including oxazepam and N-desmethyldiazepam which have elimination half-lives that far exceed the parent compound. With repeated administration, the metabolites can accumulate and result in delayed awakening, difficulty in weaning from the ventilator, and ultimately a longer length of stay once the drug is discontinued.

Midazolam is an imidazobenzodiazepine with a rapid onset of action and a short elimination half-life [62]. Its short half-life, relatively predictable pharmacokinetics, and relative lack of significant hemodynamic effects have made it a popular agent in the PICU. Availability in generic preparations also makes it a cost effective agent. A large amount of clinical experience and years of its use have demonstrated the efficacy of continuous midazolam infusions for sedation in the PICU patient at starting doses ranging from 0.05 to 0.2 mg/kg/h [63–65]. Anecdotally, it has been suggested that midazolam may not be effective during ECMO due to binding to the surface of the membrane oxygenator [65]. Additionally, as with many agents administered in the PICU, critical illness may alter the pharmacokinetics and pharmacodynamics of midazolam. Jacqz-Algrain et al. compared midazolam with placebo for sedation during mechanical ventilation in 46 infants [66]. The midazolam infusion was started at 0.06 mg/kg/h and then decreased after 24 h to 0.03 mg/kg/h in infants less than 33 weeks gestation. Midazolam provided effective sedation with only 1 of 24 patients being withdrawn from the study for inadequate sedation compared with 7 of 22 infants in the placebo group. There was a significant interpatient variation of the plasma midazolam concentration between the patients despite using

the same infusion rate. The impact of hepatic enzyme immaturity on midazolam pharmacokinetics is demonstrated by two infants with gestational ages less than 32 weeks who had plasma concentrations greater than 1,000 ng/mL.

Although intravenous administration is generally the route chosen in the PICU patient, midazolam remains unique among the various agents used for sedation in the PICU setting in that several novel routes of delivery have been reported, including oral, rectal, transmucosal (nasal, rectal, sublingual) and subcutaneous administration [67–71]. When a non-intravenous route is used, with the exception of subcutaneous administration, increased doses are required due to decreased bioavailability. The oral, rectal, and transmucosal routes have generally been used in the arena of procedural sedation or as a premedicant prior to anesthetic induction whereas subcutaneous administration has been used to allow for the slow weaning of midazolam in the prevention of withdrawal in patients who have developed physical tolerance.

Midazolam is metabolized by isoforms of the hepatic P_{450}3A enzyme system to the primary metabolite, 1-OH midazolam. The hydroxylated metabolite is equipotent with the parent compound and undergoes further hepatic metabolism via the glucuronyl transferase system to 1-OH midazolam-glucuronide. The latter is a water-soluble metabolite, which is renally excreted. In the presence of renal insufficiency, 1-OH midazolam-glucuronide accumulates, thereby potentiating the effects of midazolam [72]. Midazolam pharmacokinetics and metabolism are altered by several factors including, as noted above, post-gestational age and co-morbid conditions including hepatic disease. Alterations in protein binding, with increases in the free fraction, may occur with heparin administration, hepatic/renal dysfunction, and decreased albumin levels [73–76]. Further alterations and variability in midazolam pharmacokinetics have been reported in critically ill children [10, 77]. In a study of 21 PICU patients ranging in age from 2 days to 17 years of age, midazolam clearance in PICU patients ranging from 3 to 10 years of age was significantly longer (5.5 ± 3.5 h) than that reported in healthy age-matched children (1.2 ± 0.3 h) [10]. The authors concluded that midazolam does not demonstrate a short elimination half-life in PICU patients. They also recommended that given the prolonged half-life, a steady state serum concentration would not be achieved for approximately 20 h after starting the infusion and therefore sedation should be initiated with a bolus dose.

Lorazepam is a water-soluble benzodiazepine that unlike midazolam is metabolized by glucuronyl transferase and not the P_{450} enzyme system. As such, medications and co-morbid conditions which may alter the P_{450} system do not alter lorazepam's pharmacokinetics. Even with advanced liver disease, phase II reactions (glucuronyl transferase) are better preserved than phase I reactions (P_{450} system). The metabolites of lorazepam are pharmacologically inactive. To date the majority of experience with lorazepam use in the ICU either by intermittent bolus dosing or a continuous infusion has been in the adult population.

In an open-label trial, Pohlman et al. compared lorazepam with midazolam for sedation in 20 adult ICU patients [78]. The mean infusion rates to achieve adequate sedation was 0.06 mg/kg/h with lorazepam and 0.15 mg/kg/h with midazolam. There were fewer infusion rate adjustments per day with lorazepam than with midazolam (1.9 for lorazepam versus 3.6 for midazolam). The mean time to return to baseline mental status was also shorter with lorazepam (261 min with lorazepam versus 1,815 min with midazolam). In a blinded trial, Swart et al. similarly compared infusions of lorazepam to midazolam in 64 adult ICU patients [79]. The percent time at goal sedation score was greater with lorazepam (87 % for lorazepam versus 66 % for midazolam). The average daily dose of midazolam was 372 mg versus 23.1 mg for lorazepam leading to an average cost of approximately ten times more with midazolam. However, the latter cost issues may no longer be germaine given that generic forms of midazolam are now available. These studies, in part, led the Society of Critical Care Medicine to recommend the use of lorazepam as the preferred sedative for prolonged sedation in adults in the intensive care unit setting [80].

One interesting alternative use of lorazepam was reported by Lugo et al. who used enteral lorazepam to decrease intravenous midazolam dosing requirements and drug costs during mechanical ventilation in a cohort of 30 infants and children [81]. Sedation was initiated and maintained with midazolam until stable infusion requirements had been achieved for 24 h. Enteral lorazepam, administered every 4–6 h, was then start at a dose which was one-sixth of the total daily intravenous midazolam dose. A decrease in midazolam infusion requirements was noted on the first day and by the third day, the midazolam infusion was discontinued in 24 of 30 patients. When considering acquisition costs at the time of the study, the projected savings were over $40,000 for the 30 patients. Enteral lorazepam has also been frequently in the prevention or treatment of withdrawal following the prolonged administration of intravenous benzodiazepines for sedation during mechanical ventilation [82].

Although lorazepam has been shown to be an effective alternative to midazolam for sedation in the PICU and previously resulted in significant cost savings, prolonged infusion or repeated intermittent doses especially at higher doses, may lead to the accumulation of the diluent used in the intravenous formulations, propylene glycol [83–86]. Each mL of the lorazepam solution (2 mg/mL) contains 800 mg of propylene glycol. Signs and symptoms of propylene glycol toxicity include metabolic acidosis, renal failure/insufficiency, mental status changes, hemolysis, and an elevated osmolar gap. Propylene glycol is metabolized in the liver to lactic or excreted unchanged in the urine making toxicity more

likely in patients with renal or hepatic insufficiency. Given the immaturity of their renal and hepatic function, neonates and especially preterm infants are unable to handle propylene glycol. As such, extreme caution is recommended in this population and continuous infusions should generally be avoided. Calculation of the propylene glycol infusion rate and periodic measurement of the osmolar gap (measured minus calculated serum osmolarity) may be indicated during high dose or prolonged lorazepam infusions. Although propylene glycol concentrations can be measured by reference laboratories, they are not routinely available in most hospitals.

Etomidate

Etomidate is an intravenous anesthetic agent whose primary clinical application is the induction of anesthesia. Like many other sedative agents, etomidate exerts its effects by potentiation of the GABA inhibitory neurotransmitter system. Following intravenous administration, loss of consciousness is rapid (15–20 s) with an elimination half-life from 2.9 to 5.3 h. Recovery of consciousness, which occurs in 5–10 min following a single induction dose, is not the result of metabolic degradation, but rather rapid drug redistribution [87]. Etomidate shares the same CNS effects as propofol and the barbiturates with a reduction of the cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow (CBF), and ICP. In patients with intact cerebral autoregulation, the reduction of $CMRO_2$ results in a decrease in cerebral blood volume (CBV) and intracranial pressure (ICP). Unlike, the barbiturates or propofol, etomidate has minimal effects on cardiovascular function, thereby making it a suitable agent in patients with altered myocardial performance [88]. As opposed to the large clinical experience with the use of etomidate in the adult population, there are limited data regarding the use of etomidate in pediatric-aged patients [89–92]. Additional anecdotal experience outlines the potential utility of etomidate in pediatric patients with significant co-morbid cardiac pathology including cardiomyopathies [93, 94]. More recently, Zuckerbraun et al. reported the use of etomidate in 77 pediatric patients (average age was 8.2 years) requiring RSI in the emergency room setting [95]. Successful endotracheal intubation was achieved in all of the patients, generally with favorable hemodynamic parameters. Seven patients experienced hypotension with only two requiring resuscitative interventions.

As with the barbiturates and propofol, etomidate results in a dose-dependent depressant effect on respiratory function and can result in apnea depending on the dose used, concomitant use of other medications, and the patient's underlying status. Morgan et al. evaluated the respiratory effects of etomidate in patients pretreated with either diazepam or papaveretum and reported that the incidence of apnea was greater in the group pretreated with diazepam, suggesting that apnea is more likely with coadministration of benzodiazepines compared to opioids [96].

Etomidate appears to be a suitable agent for the induction of anesthesia in patients with reactive airway disease based on its failure in vitro to provoke histamine release from mast cells [97]. Neither propofol nor etomidate results in the smooth muscle contraction in an in vitro isolated rat tracheal myocyte preparation, while both propofol and etomidate reduce histamine-induced contraction in isolated human bronchi while altering the calcium signal in response to potassium chloride and acetylcholine [98].

In addition to its limited effects on myocardial function, the other factor that makes etomidate a valuable agent for critically ill patients is its beneficial effects on cerebral dynamics. Like the barbiturates and propofol, etomidate decreases the $CMRO_2$, resulting in cerebral vasoconstriction, decreased CBF and decreased ICP [99–101]. The reduction of $CMRO_2$ and ICP and maintenance of mean arterial pressure results in an increased cerebral perfusion pressure (CPP). The effects of etomidate on the EEG and its potential to induce seizures remain controversial. In high doses (1.28 ± 0.11 mg/kg), etomidate produces a burst suppression pattern and an isoelectric EEG [102–104]. However, anesthetic induction or sedative doses can result in EEG activation and epileptic-like EEG potentials especially in patients with underlying seizure disorders [103, 104]. Because of the potential to increase epileptogenic activity, some authors have cautioned against its use in patients with underlying seizure disorders. However, etomidate has also been used to treat refractory status epilepticus; therefore, the true clinical significance of its effects on the EEG remains unclear [105]. In addition to overt activation of the EEG, etomidate is also well known to induce myoclonic movements which may simulate tonic-clonic activity [106]. It is postulated that the myoclonic movements are of spinal origin resulting from disinhibition of inhibitory neuronal pathways. Pretreatment with fentanyl or a benzodiazepine decreases the incidence of myoclonus.

The most significant concern with etomidate, and the factor that precludes its long-term administration in the PICU setting, is its effects on the endogenous production of corticosteroids. Following its introduction into clinical practice, increased mortality was noted in patients receiving prolonged infusions of etomidate in the ICU setting [107]. Etomidate inhibits 11-β hydroxylase, a key enzyme in the production of cortisol, aldosterone, and corticosterone. This issue has also resulted in recommendations and controversy admonishing its use even as a single dose in septic patients (see below). The duration of the adrenal suppression produced by a single induction dose of etomidate has varied from study to study. Duthie et al. demonstrated a decrease in plasma cortisol levels

1 h following an induction dose of etomidate while at 24 h, no difference was noted between those patients receiving etomidate and those receiving other induction agents [108]. However, other authors have reported prolonged suppression of adrenocortical function for up to 24 h [109, 110]. In a cohort of 40 critically ill adult patients, the incidence of adrenal insufficiency, defined as a failure of the serum cortisol level to increase by 9 μg/dL after a 250 μg ACTH stimulation test, following a single dose of etomidate was 80 % at 12 h, 9 % at 48 h, and 7 % at 72 h [111]. Despite these findings, no difference in outcome was reported following etomidate administration even when there was accompanying adrenal suppression. In fact, vasopressor therapy was required less frequently and in smaller doses when etomidate was used in a cohort of 159 adult patients with septic shock [112].

The more recent concern regarding the use of etomidate in patients with sepsis stems from the CORTICUS trial, which was intended to evaluate the efficacy of corticosteroid therapy on outcome in adults with septic shock and adrenal insufficiency [113]. However, a *post hoc* analysis revealed significantly higher mortality in patients who had received etomidate. Of 96 patients who received etomidate, 60.4 % were non-responsive to corticotrophin (ACTH) and their mortality rate at 28 days was 42.7 %. Of the 403 patients who did not receive etomidate, 44.6 % were non-responsive to corticotrophin and their 28 day mortality rate was 30.5 %. The increased incidence of mortality in patients who had received etomidate was not prevented by the exogenous administration of corticosteroids (45 % versus 40 %).

Given these data, significant controversy surrounds the continued use of etomidate, with some authors calling either for elimination of its use or at least some formal re-evaluation [114–117]. As a result of these concerns, in many institutions, etomidate has been removed from the hospital formulary, the operating rooms, the emergency department and the ICU. Guidelines published by the American Academy of Pediatrics (AAP) state "etomidate should not be routinely used when intubating an infant or child with septic shock." In the case that it is used, recognition of adrenal suppression as a consequence is advocated [118]. The guidelines reference the adult CORTICUS trial and also a study led by den Brinker of mortality and adrenal function in 60 children with meningococcal sepsis [119]. Of the cohort of 60 pediatric patients, 31 required endotracheal intubation. Of these patients, 23 received etomidate and 8 did not. Patients who received etomidate had significantly lower cortisol levels, higher ACTH levels, and higher 11-deoxycortisol levels than those who did not receive etomidate. Of those that required endotracheal intubation, 7 of 23 patients who received etomidate died versus 1 of 8. Although this could suggest etomidate as a risk factor for mortality, den Brinker acknowledges it is difficult to identify the relative contribution of disease severity and endotracheal intubation with etomidate to mortality. Clinical practice guidelines for the treatment of septic shock in pediatric and neonatal patients from the American College of Critical Care Medicine state that: "Etomidate is popular as an induction agent because it maintains cardiovascular stability through blockade of the vascular K+ channel; however, even one dose used for intubation is independently associated with increased mortality in both children and adults with septic shock, possibly secondary to inhibition of adrenal corticosteroid biosynthesis [120]. Therefore, it is not recommended for this purpose."

As we progress toward the future with a re-evaluation of etomidate, prospective, randomized trials are needed with the power to determine the real question regarding etomidate which remains its effect on survival. Without such data, it may be imprudent to abandon a drug which offers significant advantages regarding its effects on myocardial performance and intracerebral dynamics. Although we are beginning to see such trials, the cohort numbers may be too small to answer the true question. Hildreth et al. prospectively randomized 30 adult trauma patients that needed RSI to receive either etomidate (0.3 mg/kg) or fentanyl (100 μg) and midazolam (5 mg) [121]. When compared to the fentanyl/midazolam group 4–6 h after endotracheal intubation, the 18 patients in the etomidate group had significantly lower cortisol levels (18.2 versus 27.8 μg/dL) and lower increases in cortisol after ACTH (4.2 versus 11.2 μg/dL). Patients receiving etomidate had longer ICU stays (6.3 versus 1.5 days), longer hospital stays (11.6 versus 6.4 days), and more ventilator days (28 versus 17 days). Tekwani et al. randomized 122 adult patients with suspected sepsis that required RSI in the emergency room to receive either midazolam (0.1 mg/kg) or etomidate (0.3 mg/kg) [122]. There was no difference in hospital length of stay, ventilator days, or mortality between the two groups.

In addition to its effects on adrenal function, infectious complications occurred in many of the patients in the initial reports involving continuous etomidate infusions. Gelb and Lok investigated the effects of clinically relevant concentrations of etomidate on white blood cell chemiluminescence, an index of oxygen free radical generation, which is an important process in white blood cell bactericidal mechanisms [123]. Neutrophils incubated in vitro with etomidate demonstrated depressed chemiluminescence suggesting that etomidate may interfere with white blood cell bactericidal activity. In addition to its effects on adrenal function, this may represent an additional mechanism responsible for the increased mortality in critically ill patients receiving etomidate.

Various other adverse effects have been reported with etomidate, which may be related to the drug itself or the diluent, including reports of anaphylactoid reactions, pain on injection, and nausea/vomiting during emergence [124–126]. Issues related to the carrier vehicle (propylene glycol)

include pain on injection, thrombophlebitis, and propylene glycol toxicity. The incidence of pain on injection that may be as high as 50 %, is greater with injection into small veins on the dorsum of the head, and can be decreased by the pre-administration of lidocaine (1.5 mg/kg) or fentanyl (2–3 μg/kg). There have been various attempts to modify the carrier vehicle to decrease the incidence of local reaction with intravenous injection. These have included decreasing the concentration of propylene glycol, use of an alcohol-based vehicle, or more recently a lipid based vehicle. The latter has been shown to significantly reduce the incidence of pain on injection and thrombophlebitis with administration through a peripheral vein [127]. Given the myriad of issues with etomidate, most notably its effects on corticosteroid production, there is ongoing debate as to whether it should be used at all in critically ill patients. Of note, Carbo-etomidate, an analogue of etomidate with similar hypnotic properties and cardiovascular stability, does suppress steroid synthesis in animal studies and thus may be a promising alternative for critically ill patients [128].

Ketamine

Ketamine, introduced into the clinical practice of medicine in the 1960s, is a phencyclidine derivative that remains classified as an intravenous anesthetic agent [129]. It produces dissociative anesthesia which refers to the state induced in which patients may keep their eyes open and yet be amnestic and unresponsive to painful stimuli. A unique attribute of ketamine, which separates it from the majority of other agents used for sedation, is the provision of both amnesia and analgesia. Ketamine's clinical effects are likely from interactions at several receptor sites, most notably agonism at opioid and muscarinic receptors as well as antagonism at NMDA receptors. Given its effects at the opioid and NMDA receptors, there is growing interest in the role of ketamine for the management of acute and potentially chronic pain. In the adult population following major surgical procedures, a low dose ketamine infusion or its inclusion with morphine in the PCA-solution has been shown to result in a similar level of analgesia with a decrease in the total opioid consumption [130–132].

Ketamine contains a chiral carbon in its structure and in the United States is available as a racemic mixture of the two optical isomers [S(+) and R(−)]. In many countries, the isolated isomer [S(+)] is available for clinical. Metabolism of ketamine occurs primarily by hepatic N-methylation to norketamine, which is further metabolized via hydroxylation pathways with subsequent urinary excretion. Norketamine retains approximately one-third of the analgesic and sedative properties of the parent compound. With oral administration, greater first past metabolism occurs with the production of norketamine which accounts for a significant portion of the clinical effects with the oral route. Regardless of the route of administration, with repeated dosing or a continuous infusion, dose reductions are suggested in patients with hepatic dysfunction. Additionally, as norketamine is dependent on renal elimination, dose modifications are also suggested with renal insufficiency or failure.

Beneficial properties of ketamine include preservation of cardiovascular function in most clinical scenarios, limited effects on respiratory mechanics, and maintenance of central control of ventilation in the majority of patients. Given these properties, it is frequently chosen for painful, invasive procedures in the spontaneously breathing patient [133]. For this purpose, incremental doses (0.5–1 mg/kg) are administered every 1–2 min and titrated to achieve the desired level of sedation and analgesia. Although the need for the practice has been questioned, the time-honored practice has been for the administration of an anti-sialogogue such as glycopyrrolate to prevent salivation. A benzodiazepine or dexmedetomidine is frequently co-administered to limit the occurrence of emergence phenomena. The latter are more common in the adolescent and older age groups (see below).

Ketamine's popularity as an induction agent for endotracheal intubation in the anesthesia and critical care arena relate to its beneficial effects on cardiorespiratory function. In most clinical situations, ketamine administration results in an increase in heart rate and an increase or maintenance of blood pressure. These hemodynamic effects are mediated indirectly through the sympathetic nervous system and the release of endogenous catecholamines [134]. This effect also account for ketamine's bronchodilatory properties. Although the indirect sympathomimetic effects from endogenous catecholamine release generally overshadow ketamine's direct negative inotropic properties, hypotension and even cardiovascular collapse may occur in patients with diminished myocardial contractility when the endogenous catecholamine stores have been depleted by chronic illness or comorbid conditions [135, 136].

An issue of controversy with ketamine remains its effects on pulmonary vascular resistance (PVR) with conflicting results reported in the medical literature [137–140]. Although older studies suggested that ketamine increased PVR, these evaluations were performed during spontaneous ventilation. Although the respiratory effects are generally minimal, the alterations in PVR may have been related to alterations in the $PaCO_2$ and not a direct effect of ketamine on the pulmonary vasculature. More recently, Williams et al. demonstrated no change in hemodynamic parameters including pulmonary artery pressure and PVR in a group of pediatric patients with pre-existing pulmonary hypertension undergoing cardiac catheterization [141]. Additional support for the safety of ketamine in patients with congenital heart disease is provided by the significant experience with its use during

spontaneous ventilation for sedation during cardiac catheterization [142, 143]. Lebovic et al. reported less hypotension with ketamine compared with propofol, although the recovery times were significantly longer with ketamine [143].

An additional property of ketamine which results in its popularity for sedation during spontaneous ventilation are its limited effects on respiratory parameters including functional residual capacity, minute ventilation, and tidal volume [144]. Endogenous catecholamine release also generally results in improved pulmonary compliance, decreased resistance to airflow, prevention and at times reversal of bronchospasm [145]. Although minute ventilation is generally maintained, hypercarbia and a rightward shift of the CO_2 response curve may occur [146]. Although ketamine is generally useful for procedural sedation in that protective airway reflexes and spontaneous ventilation are maintained, like all of the agents discussed in this chapter, ketamine can result in loss of protective airway reflexes with the aspiration of gastric contents, upper airway obstruction, and even apnea [147, 148] Airway patency and the potential for airway obstruction or laryngospasm may also result from increased oral secretions. Despite this, anecdotal experience has suggested the utility of ketamine for sedation of infants during flexible fiberoptic bronchoscopy during spontaneous ventilation [149].

An additional area of controversy surrounding ketamine is its effects on intracerebral dynamics with early studies suggesting that ketamine increased CBF and ICP [150, 151]. These clinical studies were supported by animal studies demonstrating that the alterations in ICP resulted from direct cerebral vasodilatation, which was mediated through central cholinergic receptors [152, 153]. However, it has been postulated that the increased ICP associated with ketamine administration was more likely an indirect effect related to changes in $PaCO_2$ rather than a direct effect on the cerebral vasculature. Furthermore, conflicting data are reported from other animal studies showing no change or even a decrease in ICP following ketamine administration [154, 155]. In these later studies, the animals received mechanical ventilation to maintain a normal normocarbia. No change or even a decrease in ICP has been reported in adults with traumatic brain injury following the administration of ketamine [156, 157]. In 30 pediatric patients with severe traumatic brain injury, a total of 82 doses of ketamine were given to treat ICP elevations greater than 18 mmHg [158]. Following the bolus dose of ketamine (1–1.5 mg/kg), ICP not only decreased by 30 % (from 25.8 ± 8.4 to 18.0 ± 8.5 mmHg, $p < 0.001$), but CPP increased from 54.4 ± 11.7 to 58.3 ± 13.4 mmHg, $p < 0.005$.

An additional effect that has been described with ketamine, which may make it a beneficial agent in patients with CNS trauma, is an alteration of transmembrane calcium and magnesium [159]. With injury or trauma to the CNS trauma, the release of excitatory neurotransmitters alters calcium currents leading to an increase in the cytoplasmic calcium concentration and the potential for delayed neuronal necrosis. The latter is commonly referred to secondary injury which may result in significant progression of CNS injury following trauma. Through its antagonism at the NMDA receptor, ketamine has been shown to block the influx of calcium and lower cytoplasmic calcium concentrations [159]. Whether this effect will result in prevention of secondary injury following brain trauma has been not been conclusively demonstrated.

Another controversial issue related to the CNS effects of ketamine is its use in patients at risk for or with an underlying seizure disorder. EEG recordings in children or laboratory animals during ketamine administration demonstrate increased frequency and amplitude with occasional paroxysmal seizure-like activity [160, 161]. These EEG effects of ketamine account for the inaccuracy of the BIS monitor in judging the depth of sedation or anesthesia with ketamine (see above). However, no clinical evidence of seizure activity has been reported with ketamine administration while studies in laboratory animals have demonstrated an anticonvulsant effect of ketamine [162, 163]. There is also at least one clinical report describing the administration of ketamine for the treatment of refractory status epilepticus [164].

With everyday clinical use, the adverse effect of ketamine that raises the most concern tends to be its potential to cause emergence phenomena or hallucinations. It has been postulated that emergence phenomena result from the alteration of auditory and visual relays in the inferior colliculus and the medial geniculate nucleus leading to the misinterpretation of visual and auditory stimuli [165]. Because of these concerns, some practitioners prefer to avoid the routine use of ketamine in older pediatric patients including adolescents in whom emergence phenomena are more common. Alternatively, the pre- or concomitant administration of a benzodiazepine (lorazepam or midazolam), barbiturate or even dexmedetomidine prior to or with ketamine can markedly diminish the incidence of such problems. As noted above, ketamine is a racemic compound with the commonly used solution a mixture of the two optical isomers, [S(+)] and [R(−)]. The [S(+)] enantiomer is more potent than the racemic mixture and although the clinical studies are not conclusive, it has been suggested that it may have fewer of the psychomimetic effects than the racemic mixture [166].

While there is ample experience with ketamine in pediatric procedural sedation arena, there are limited reports regarding its use by continuous infusion for sedation of PICU patients during mechanical ventilation [167–169]. Hartvig et al. used a ketamine infusion to provide sedation and analgesia following cardiac surgery in ten pediatric patients who ranged in age from 1 week to 30 months [168]. The patients received an infusion of either 1 or 2 mg/kg/h. Supplemental doses of midazolam were administered as needed. The two groups had similar and acceptable levels of

sedation. No adverse effects were noted. More recently, there has been interest in the potential utility of ketamine in delaying the onset and severity of opioid tolerance during prolonged infusions in the PICU setting. Although preliminary animal data have demonstrated the potential utility of NMDA antagonists in delaying tolerance, the limited data in the pediatric population have failed to show the utility of ketamine for this purpose [170].

A final concern with the clinical use of ketamine is that it is commercially available in three different concentrations (100 mg/mL, 50 mg/mL and 10 mg/mL) and therefore inadvertent over or underdosing is possible without careful consideration of its concentration. The 100 mg/mL solution is meant for IM or PO administration to minimize the volume required while the more dilute solutions (10 mg/mL) lend themselves readily to the small incremental intravenous doses needed for procedural sedation.

Although it may never become a first-line agent for sedation in the PICU patient during mechanical ventilation, ketamine may be useful in various scenarios including: (i) patients who develop adverse cardiovascular effects with opioids or benzodiazepines, (ii) the provision of sedation with the preservation of spontaneous ventilation when using non-invasive ventilation techniques, (iii) patients with status asthmaticus in whom the release of endogenous catecholamines following ketamine administration may provide some therapeutic impact, and (iv) during the performance of brief, painful invasive procedures in the spontaneously breathing patient (see above). As with midazolam, several alternative routes of delivery have been reported with ketamine including oral and transmucosal (nasal, rectal) administration. These alternative routes of delivery have been used for one time dosing of the agent for sedation during a procedure or as a premedicant to anesthetic induction and will have a limited role for ongoing sedation of the PICU patient.

Propofol

Propofol is an alkyl phenol compound with general anesthetic properties. Its chemical structure is distinct from that of other intravenous anesthetic agents such as the barbiturates and etomidate, although its mechanism of action is similar by acting through the GABA system [171]. Propofol facilitates the binding of GABA to specific membrane-bound receptors which are distinct from those of the barbiturates and the benzodiazepines. The end result of this interaction is increased chloride conductance and neuronal hyperpolarization. Although initially introduced into anesthesia practice for the induction and maintenance of anesthesia, its rapid onset, rapid recovery time, and lack of active metabolites led to its evaluation as an agent for ICU sedation [172, 173]. When compared with midazolam or intermittent lorazepam for sedation in adult patients, propofol has been shown to provide shorter recovery times, improved titration efficiency, reduced post-hypnotic obtundation, and faster weaning from mechanical ventilation [174, 175].

Like the barbiturates and etomidate, propofol decreases $CMRO_2$ leading to reflex cerebral vasoconstriction, decreased CBF & CBV with a lowering of ICP [176]. The potential beneficial effects of propofol on intracerebral dynamics have been confirmed in several animal studies [177, 178]. Despite these animal data, there are conflicting results in regards to the effects of propofol on ICP from studies in humans [179–182]. Although ICP is decreased in the majority of the studies, propofol also lowers MAP resulting in a decrease of the CPP. In patients with intact autoregulation of CBF, a decrease in CPP leads to reflex cerebral vasodilation to maintain CBF, which can secondarily increase CBV and ICP if intracranial compliance is altered. The resultant cerebral vasodilatation negates the decrease in ICP related to the decrease in $CMRO_2$ induced by propofol. However, if the MAP is maintained at baseline with the use of a vasopressor, propofol lowers ICP and increases CPP [183, 184]. Although generally chosen as an anesthetic induction because of its beneficial effects on emergence time, propofol may also be a valuable agent in patients at risk for airway reactivity. In both asthmatic and non-asthmatic patients, the incidence of wheezing was shown to be lower when anesthetic induction was performed with propofol (2.5 mg/kg) compared to either thiopental/thiamylal (5 mg/kg) or methohexital (1.5 mg/kg) [185]. Propofol's beneficial effects on airway reactivity are supported by animal studies showing the attenuation of carbachol-induced airway constriction in canine tracheal smooth muscle and prevention of reflex bronchoconstriction to several provocative agents in isolated guinea pig trachea smooth muscle [186, 187]. However, these airway effects may not be shared by all preparations of propofol. In both an animal study and a human study by Rieschke et al., the beneficial effects on airway reactivity were present only with the propofol solution that contained EDTA as the preservative and not the formulation containing sodium metabisulphite [188, 189].

Propofol's cardiovascular effects resemble those of the barbiturates with the potential for hypotension from peripheral vasodilation and negative inotropic properties [190]. These effects are accentuated following rapid bolus administration and in patients with compromised cardiovascular function and co-morbid cardiac diseases. The peripheral vasodilatation may be particularly detrimental in patients with a fixed stroke volume such as is seen with aortic or mitral stenosis. The adverse hemodynamic profile of propofol administration can be prevented by the administration of calcium chloride (10 mg/kg) [191]. Additional cardiovascular effects may be caused by augmentation of central vagal tone leading to bradycardia, conduction disturbances, and

asystole [192, 193]. The latter tend to be more common with the concomitant administration of other medications that alter cardiac chronotropic function (fentanyl or succinylcholine). In rare circumstances, the augmentation of vagal tone has resulted in a therapeutic effect and the termination of supraventricular arrhythmias [194]. The combination of ketamine-propofol, commonly known as ketofol, has gained popularity in the arena procedural as another means of limiting the adverse effect profile of propofol especially its hemodynamic effects. When used for procedural sedation in the pediatric emergency room and operating room the combination of these two agents has been shown to have a lower incidence of adverse hemodynamic effects while providing excellent sedation [195–197]. This is especially true for painful procedures as propofol has limited analgesic properties. Ketamine and propofol can be administered individually or combined in one syringe to provide a mixture containing 3–5 mg/mL ketamine and 10 mg/mL propofol. For brief procedures, incremental doses of 0.1 mL/kg of the solution can be administered resulting in the delivery of 0.3–0.5 mg/kg of ketamine and 1 mg/kg of propofol.

Various neurological manifestations have been reported with the administration of propofol including opisthotonic posturing, myoclonic movements (especially in children), and seizure-like activity [198–200]. Movement disorders including myoclonus and posturing have been attributed to propofol's antagonism at glycine receptors in subcortical structures. Although there are anecdotal reports with a temporal relationship between propofol and what appeared to be clinical seizure activity [200], no formal evidence exists to prove this association. In a study evaluating the effects of propofol and thiopental on the surface electroencephalograms of 20 patients undergoing temporal lobe surgery, no difference in the rate of discharge or extension of the irritative zone was seen [201]. Furthermore, given its effects on the electroencephalogram, propofol remains an integral part of various algorithms for treating patients with refractory status epilepticus [202, 203].

Despite its benefits and efficacy, the routine use of propofol by continuous infusion for sedation of the PICU patient is not recommended and in fact, is considered contraindicated by many because of reports of the "propofol infusion syndrome" and potentially other adverse effects (Table 3.4). The latter refers to a constellation of signs and symptoms that includes metabolic acidosis, bradycardia, dysrhythmias, rhabdomyolysis, and fatal cardiac failure [204–206]. The first reports of the propofol infusion syndrome were published in 1992 [204]. Subsequently, a larger series of 18 children who developed propofol infusion appeared in the literature [207]. Potential risk factors in the cohort of 18 pediatric patients included propofol administration for more than 48 h and/or infusion rates greater than 4 mg/kg/h. Not all patients seemed uniformly susceptible suggesting that there may be an underlying co-morbid condition or genetic predisposition responsible for the development of the propofol infusion syndrome. Another associated feature was age as 13 of the 18 patients were 4 years of age or younger and only 1 of 18 was more than 10 years of age. Following the initial reports in the pediatric population, the syndrome has been reported in older patients including a 17 year-old adolescent and even in the adult population [208, 209]. In addition to the metabolic acidosis and cardiovascular manifestations, additional signs and symptoms have included lipemic serum, hepatomegaly, and muscle involvement with rhabdomyolysis and hyperkalemia. The suggested treatment includes the immediate discontinuation of the propofol combined with symptomatic treatment of cardiovascular dysfunction and acidosis. The etiology of the propofol infusion syndrome has been linked to mitochondrial dysfunction in susceptible patients. In a guinea pig cardiomyocyte preparation, propofol has been shown to disrupt mitochondrial function [210]. Biochemical analysis of a patient who developed the propofol infusion syndrome revealed an increase in the concentration of C_5-acylcarnitine and an increased plasma concentration of malonyl-carnitine indicative of inhibition of mitochondrial function at complex II of the respiratory chain [211]. The latter compound inhibits the transport protein necessary for the movement of long-chain fatty acids into the mitochondria. Hemofiltration was used in the treatment of this patient, which resulted in reversal of the clinical manifestations and the patient's recovery. Similar findings with an elevated serum concentration of acylcarnitine were reported in a 5-month-old who developed propofol infusion syndrome [212]. Treatment with charcoal hemoperfusion resulted in resolution of the signs and symptoms.

In specific circumstances, propofol may be used as a therapeutic tool in the treatment of refractory status epilepticus, increased ICP or a short-term bridge to extubation in high-risk children [213]. In such cases, intermittent laboratory analysis of plasma lactate concentration, acid-base status, and creatinine phosphokinase (evaluating for rhabdomyolysis) is suggested to monitor for the development of propofol infusion syndrome. If a base deficit is noted with an increasing serum lactate, immediate discontinuation of propofol is recommended.

Table 3.4 Adverse effects described with propofol

Hypotension (negative inotropic effect, vasodilation, bradycardia)
Respiratory depression and apnea
Neurologic sequelae (opisthotonic posturing, seizure-like activity, myoclonus)
Anaphylactoid reactions
Propofol infusion syndrome
Pain on injection
Bacterial contamination of solution
Hyperlipidemia and hypercarbia
Potential for depletion of trace elements including zinc

Despite the previously outlined concerns with propofol, the contention that we should abandon its use for sedation of the PICU has not been universally embraced by the medical community with the contention that is has been used safely and effectively for sedation in small cohorts of PICU patients [214–217]. The decision regarding the propofol controversy should be considered in context of a letter issued in March 2001 by AstraZeneca, the manufacturers of Diprivan™, one of the two commercially available propofol preparations [218]. The letter outlined the results of a clinical trial comparing propofol (either a 1 % or 2 % solution) to other agents used for PICU sedation. There were 12 (11 %) deaths in the 2 % propofol group, 9 deaths (8 %) in the 1 % propofol group and 4 deaths (4 %) in the standard sedation group. Although subsequent review did not show a specific pattern to the deaths, there was enough concern that the company concluded "propofol is currently not approved for sedation in pediatric ICU patients in the United States and should not be used for this purpose". Issues regarding the propofol infusion syndrome should not limit its use in the operating room arena or for procedural sedation. However, as with the majority of sedative and analgesic agents, propofol can cause respiratory depression and apnea. Clinical reports regarding its use for procedural sedation demonstrate a relatively high incidence of respiratory effects including hypoventilation, upper airway obstruction, and apnea, many of which required bag-mask ventilation or repositioning of the airway [219].

Additional problems with propofol relate to its delivery in a lipid emulsion (the same lipid preparation that is used in parenteral hyperalimentation solutions). Problems with the lipid component include anaphylactoid reactions, pain on injection, and elevated triglyceride levels or hypercapnia with prolonged infusions [220–222]. The issues regarding the use of propofol in egg-allergic patients remains somewhat controversial with many healthcare providers believing that propofol should not be used in such patients. All propofol preparations with the exception of newly available fospropofol (see below) are lipid suspensions that contain egg lecithin-phosphatide and soy oil. In many countries, a history of hypersensitivity to egg and soy are listed as contraindications in the manufacturer's product information. However, recent work has challenged this contention with the demonstration that propofol did not cause problems except in patients with true egg anaphylaxis [223].

The lipid content of propofol must be considered when calculating the patient's day caloric intake. A propofol infusion of 2 mg/kg/h provides approximately 0.5 g/kg/day of fat. In an attempt to lessen such problems, a 2 % solution of propofol (twice the amount of propofol with the same amount of lipid per mL as the 1 % solution) has undergone clinical evaluations. To date, this preparation is not available in the United States. Although the 2 % propofol solution has been shown to decrease the incidence of hypertriglyceridemia, there may be an alteration of the drug's bioavailability as there was an increased dose requirement and an increased number of patients with inadequate sedation when the 2 % solution is compared with the 1 % solution [224, 225].

Pain with the injection of propofol remains a significant complaint especially when small veins on the dorsum of the hands or feet are used. Variable success in decreasing the incidence of pain has been reported with various maneuvers including the preadministration of lidocaine, mixing the lidocaine and propofol in a single solution, mixing the propofol with thiopental, diluting the concentration of the propofol, cooling it prior to bolus administration, or the administration of a small dose of ketamine (0.5 mg/kg) prior to the administration of propofol [226–230]. As noted above, the co-administration of propofol and ketamine is being more popular in the arena of procedural sedation. Since propofol has limited analgesic properties, ketamine and propofol can be administered together to take advantage of the analgesia provided by ketamine and the rapid recovery with propofol.

Another issue with the lipid component of propofol is its potential to serve as a viable growth media for bacteria with reports of bacteremia and postoperative wound infections linked to extrinsically contaminated propofol [231, 232]. The currently available propofol solutions contain a preservative which should serve to limit these problems. The commercially available propofol solutions contain either disodium EDTA (ethylenediaminetetraacetic acid), sodium metabisulfite, or benzyl alcohol as a preservative. Clinical trials have raised concerns as to whether the physiologic effects of these preparations are equivalent. Issues related to their differential effects on airway reactivity have been previously discussed. The literature contains contrasting information regarding the anesthetic potency of the two preparations. A retrospective analysis of dose requirements during sedation for MRI demonstrated a decreased potency of the sodium metabisulfite propofol solution when compared to the EDTA solution [233]. However, when compared using depth of anesthesia monitoring (bispectral index), no difference in the cardiovascular or hypnotic effects of the solutions was noted [234].

A more recent addition to the pharmacology arena is fospropofol, a prodrug that release propofol when metabolized. As a prodrug of propofol, intravenous fospropofol is metabolized by alkaline phosphatases to produce propofol, phosphate and formaldehyde [235, 236]. The primary advantage of this new formulation includes its water solubility, the lack of the need for the lipid vehicle and hence the elimination of adverse effects related to it. When compared to propofol, the onset of the clinical effect and recovery from fospropofol is longer. Given that it is a prodrug and is metabolized following intravenous administration, fospropofol produces a

gradual increase in the plasma propofol concentration. This is followed by a gradual decrease over time with a longer effective time with a therapeutic blood concentration of propofol. These properties may be useful in clinical conditions that do not require an immediate onset of action but rather a more prolonged effect over time. Although the initial clinical experience has been for procedural sedation, recent work has also evaluated its efficacy in the ICU population [237, 238]. To date, there is no information regarding its use in the pediatric age range.

Barbiturates

The barbiturates can be classified according to their chemical structure or their duration of activity. The central ring structure varies in that it can contain a sulfur atom (thiobarbiturates such as thiamylal and thiopental) or an oxygen atom (oxybarbiturate such as methohexital). Short-acting agents such as methohexital, thiopental, and thiamylal have a clinical duration of action of 5–10 min. Long-acting agents with half-lives of 6–12 h include pentobarbital and phenobarbital. As with other intravenous anesthetic agents, the short duration of the effect following a single intravenous bolus results from rapid redistribution and not from metabolism. The short-acting barbiturates are used most commonly by intravenous, bolus administration for brief procedures such as endotracheal intubation. In rare circumstances when a more prolonged effect is needed either for sedation or other therapeutic effects, a continuous infusion of these agents is required to maintain plasma concentrations. When this is done, the determination of the offset time shifts from redistribution to hepatic metabolism. As such, there will also be markedly prolonged duration of action which is dependent on the duration of the infusion.

The barbiturates were first introduced into clinical practice in the 1940s for the induction of anesthesia. Although a generally safe and effective agent, many deaths were attributed to their profound negative inotropic effects which can be exaggerated in patients with co-morbid cardiovascular disease or in the setting of hypovolemia. These properties led to a very high incidence of cardiac arrest in trauma patients during World War II and the suggestion that the use of these medications be abandoned. However, a better understanding of the physiology and pharmacology of the short-acting barbiturates has led to their safe use over the past 50–60 years for the induction of anesthesia. More recently, supply issues have eliminated the use of the short-acting barbiturates such as thiopental for the induction of anesthesia. These agents are currently manufactured only in Italy and as these agents are used for lethal injection in the United States, countries such as Italy who do not condone such practices will not export the barbiturates to the United States.

Given their long history of clinical use and availability, the intermediate acting barbiturates such as pentobarbital remain a popular agent for sedation particularly during non-invasive radiologic procedures such as computed tomography or magnetic resonance imaging [239, 240]. Methohexital has also been used via the rectal route to provide sedation during non-invasive radiologic procedures such as CT imaging [241, 242].

In the PICU setting, the barbiturates are rarely if ever used for continuous sedation (see below). A more common reason for their use is based on their beneficial physiologic effects including decreased $CMRO_2$ with cerebral vasoconstriction and decreased CBF leading to decreased ICP [243, 244]. The barbiturates have also be used in the treatment of refractory status epilepticus while animal studies have demonstrated their potential to provide cerebral protection during periods of cerebral hypoxia or hypoperfusion [245–248].

The role for and reports of the barbiturates for continuous sedation in the pediatric patient during mechanical ventilation is definitely limited [249, 250]. In these anecdotal reports, pentobarbital was used when conventional agents including the opioids and benzodiazepines had failed. Despite their efficacy even during difficult sedation scenarios such as the older patient during ECMO, a relatively high incidence of adverse effects has been noted. Yanay et al. in a retrospective review of pentobarbital sedation for eight PICU patients noted that although pentobarbital provided effective sedation and allowed the discontinuation of neuromuscular blocking agents, there was a relatively high incidence of adverse effects [251]. Adverse effects were noted in five of the eight patients (62.5 %) and included blood pressure instability (two of eight), oversedation (one of eight), and neurologic sequelae (one of eight) including withdrawal phenomena. These adverse effects led to discontinuation of the drug in two of the eight patients.

The barbiturates' effects on cardiorespiratory function are dose-dependent. In healthy patients, sedative doses have limited effects on cardiovascular function, respiratory drive, and airway protective reflexes, while larger doses, especially in patients with co-morbid cardiac or respiratory compromise, may result in respiratory depression, apnea or hypotension. Hypotension results from both peripheral vasodilation and a direct negative inotropic effect. The effects on cardiovascular and ventilatory function are additive with other agents such as opioids. Additional concerns relate to the fact that the barbiturate solution is alkaline leading to incompatibilities with other medications and parenteral alimentation solutions, thereby necessitating a separate infusion site. As the pH of the barbiturate solution is high, local erythema and thrombophlebitis can occur with subcutaneous infiltration. The barbiturates possess no analgesic properties and therefore should be used with an opioid in situations requiring analgesia. In some cases barbiturate dosing is associated

with a paradoxical reaction associated with restlessness, excitement and delirium. This effect can be reversed with the oral or intravenous administration of caffeine [252].

Opioids

The opiates are a mainstay for alleviating pain in the PICU patient and remain a commonly used agent to provide sedation during mechanical ventilation. These agents are frequently used secondary to their potent respiratory depressant effects to blunt the endogenous respiratory drive, improve patient-ventilator synchrony and thereby facilitate mechanical ventilation. Opiates elicit their action by interactions with mu, delta, and kappa receptors that are present throughout the CNS and peripheral tissue [253]. Although these agents provide analgesia, even with high doses (fentanyl 50–75 μg/kg) amnesia is not ensured.

Morphine is a frequently used as well as extremely effective agent for sedation and analgesia in the PICU setting. Although concern has been expressed regarding the potential neuroapoptotic and long-term effects of agents that are GABA-agonists or NMDA-antagonists, the current data demonstrates no concern regarding the long term neurocognitive effects of morphine [254–257]. Morphine undergoes glucuronidation in the liver that with the production of two major metabolites, morphine-3-glucoronide and morphine-6-glucuronide. The latter has significant analgesic properties as well as respiratory depressant effects. Morphine metabolites are excreted by the kidney and may therefore accumulate in patients with decreased renal function. Given its dependence on hepatic metabolism, there may be a significant prolongation of its effect and decreased clearance in the preterm and term neonate related to maturational issues of the hepatic microsomal enzymes.

As morphine has a decreased affinity for the opiate receptor when compared to synthetic opiates (fentanyl), it results in a lesser degree of tolerance thereby offering an advantage over the commonly used synthetic opioids [258]. In a cohort of infants requiring sedation and analgesia during ECMO (mean duration of ECMO 4–5 days), morphine was found to provide equivalent levels of sedation compared to fentanyl, while decreasing the need for supplemental bolus doses of opioid [259]. Infants receiving morphine had a lower incidence of withdrawal (13 of 27 with fentanyl versus 1 of 11 with morphine, $p<0.01$) and were hospitalized for fewer days after ECMO (31.1 ± 14 versus 21.5 ± 7.0 days, $p=0.01$).

Morphine's cardiovascular effects include dilation of the venous capacitance system and a modest decrease in blood pressure. The latter may be exaggerated in patients with decreased intravascular volume or co-morbid cardiovascular dysfunction. Historically, the venodilatory effects of morphine have been used in adults with heart failure and pulmonary edema as a means of reducing venous return (preload) thereby resulting in a decrease in left ventricular end-diastolic volume and pulmonary congestion.

Infusions of 10–30 μg/kg/h have been shown to provide morphine plasma concentrations of 10–22 ng/mL and effective analgesia and sedation during mechanical ventilation after surgery for CHD, without impairing the ability to wean mechanical ventilatory support [260]. However, when comparing a morphine infusion of 10–30 μg/kg/h morphine infusions to saline infusions in 898 preterm infants, morphine infusions led to a significantly longer duration of ventilation (7 days [4–20 days] versus 6 days [3–19 days], $p<0.01$) [261].

Hydromorphone is a morphine derivative with a potency eight to ten times that of morphine. It has a similar volume of distribution and duration of action to morphine and also undergoes glucuronidation metabolism. Unlike morphine, hydromorphone does not cause histamine release thereby limiting its potential to cause pruritus. As pruritus from morphine appears to be particularly prevalent in the adolescent and young adult population, in our clinical practice, hydromorphone is generally chosen as the first-line agent for patient-controlled analgesia in these populations. Like morphine, hydromorphone undergoes hepatic metabolism; however as its metabolites are inactive, it can be used in patients with renal dysfunction.

In current clinical practice, the commonly used synthetic opioids include fentanyl, sufentanil, alfentanil, and remifentanil. Given their limited effects on myocardial function, the synthetic opioids continue to be frequently used agents for sedation during mechanical ventilation, especially in neonates and infants. In patients with altered myocardial function or at risk for pulmonary hypertension such as an infant with a large preoperative left-to-right shunt, the synthetic opioids provide cardiovascular stability, beneficial effects on pulmonary vascular resistance, and effective blunting of sympathetic stress. Due to their prompt redistribution and resultant short plasma half-lives following bolus administration, synthetic opioids are generally administered by a continuous infusion to maintain plasma concentrations adequate to provide analgesia.

Fentanyl is the least expensive of the synthetic opioids and the one with which there is the most clinical experience in the PICU setting. On the other hand, remifentanil is the most expensive of the synthetic opioids. Fentanyl, sufentanil, and alfentanil are dependent on hepatic metabolism. Specific clinical scenarios decrease hepatic metabolism and thereby prolong the half-life of these agents including immaturity of the hepatic microsomal enzymes as is seen in term and especially preterm infants and decreased hepatic blood flow which occurs following intra-abdominal procedures. Although these agents are short-acting when administered as a single bolus dose, like midazolam they have a

context sensitive half-life so that the duration of their effect is prolonged when they are administered over an extended period of time.

Remifentanil is unique among the synthetic opioids in that it is metabolized by non-specific esterases in the plasma, with a clinical half-life of 5–10 min and a brief duration of effect even following 12–24 h of continuous infusion [262]. These pharmacokinetic parameters hold true even in the neonatal population, making remifentanil the only opioid whose pharmacokinetics are not altered by gestational or chronologic age [263]. Remifentanil is 150–200 times more potent than morphine. Given these properties, it is a potentially useful agent for providing a deep level of sedation and yet allowing for rapid awakening upon discontinuation of the infusion [264]. When comparing an analgesia-based sedation regimen (remifentanil infusion) to a standard hypnotic-based regimen (midazolam infusion) in adult ICU patients, those receiving remifentanil had a reduction in ventilator days [265]. In contrast, a subsequent study demonstrated no difference in time to tracheal extubation when remifentanil/propofol was compared to fentanyl/propofol while patients in the remifentanil group complained of more pain [266].

In the PICU, reports of remifentanil use are limited [267, 268]. Welzing et al. reported a pilot study involving 23 intubated children who ranged in age from 3 months to 10 years [267]. The sedation regimen was transitioned from fentanyl and midazolam infusions to remifentanil and propofol during the final stages of weaning from mechanical ventilation [267]. When the remifentanil was discontinued, there was a rapid transition from hypnosis to appropriate alertness with regular spontaneous breathing. The patients underwent tracheal extubation an average of 24 min (5–80 min) following discontinuation of the remifentanil infusions. Similar efficacy in providing a deep level of sedation and yet rapidly allowing emergence from sedation and successful tracheal extubation was reported in an anecdotal series of four pediatric patients with potential airway issues [268].

Despite the preliminary successes with remifentanil, issues to be considered include its cost, the potential for the rapid development of withdrawal when the infusion is discontinued if patients are tolerant to other agents used for sedation, and the rapid development of tolerance to remifentanil which may necessitate rapid dose escalations. Work in adult volunteers has demonstrated the development of tolerance to remifentanil after only 60–90 min [269]. In the clinical arena, this has translated into greater postoperative opioid requirements when remifentanil is used intraoperatively and the need to escalate doses rapidly when remifentanil is used for ICU sedation [270, 271]. The magnitude of tolerance and the rate at which it develops appears to be related more to the pharmacokinetics of the agent than its potency, with tolerance developing more rapidly with short-acting agents [271, 272].

Two additional issues relevant to the synthetic opioids are potential ICP effects and chest wall rigidity. In adult patients with altered intracranial compliance, the administration of fentanyl has been shown to result in a decrease in the mean arterial pressure, an increase in ICP, and a decrease in CPP [273]. The mechanism responsible for this effect has been shown to be a reflex cerebral vasodilation in response to the decrease in MAP [274]. When the mean arterial pressure is maintained with a direct-acting vasoconstrictor, no change in ICP is noted, thereby making these agents safe and effective in patients with closed head injury and other pathologies that may alter intracranial compliance.

Another adverse effect specific to the synthetic opioids is chest wall rigidity [275, 276]. The incidence of chest wall rigidity is related to the dose, rate of administration, and perhaps the age of the patient. It is a centrally-mediated, idiosyncratic reaction which, when severe, can interfere with effective respiratory function. It can be reversed with naloxone or interrupted with neuromuscular blocking agents. However, both effects may take 1–2 min to work during which time, profound hypoxemia can result in cardiovascular instability especially in the neonate. Although chest wall rigidity is generally encountered when large doses of fentanyl (50 μg/kg) administered at the time of anesthetic induction for cardiac surgery in adults, it has also been reported in both term and preterm neonates at much lower doses [277, 278]. In the series reported by Fahnenstich et al., chest wall rigidity followed by hypercapnia, hypoxemia, and then bradycardia was noted following doses of 3–5 μg/kg [277]. In two of the patients, endotracheal intubation was impossible due to laryngospasm. Chest wall rigidity was reversed in less than 1 min by the administration of naloxone (20–40 μg/kg). These examples suggest that in neonates it is particularly important to adhere to dosing guidelines recommending that these drugs be administered slowly and in small increments while titrating to effect. Although chest wall rigidity is a rare phenomenon, its occurrence should be considered if respiratory dysfunction is noted following the use of synthetic opioids.

Although administered most commonly via the intravenous route, rare circumstances such as limited intravenous access or drug incompatibilities may occur which preclude intravenous administration. In such situations, the subcutaneous administration of opioids is feasible. Although used most commonly in the control of chronic cancer pain, there is anecdotal experience with the use subcutaneous opioid infusions in the ICU setting [279, 280]. Bruera et al. successfully used subcutaneous opioids administered by intermittent dosing or continuous infusions for a total of 60 patient days in adult ICU patients [280]. The infusions were delivered through a 25-gauge butterfly needle inserted subcutaneously in the subclavicular area or the anterior abdominal wall. No infectious complications were noted and the insertion site

was changed only three times due to local problems such as erythema. Although the authors expressed a theoretical concern over possible delays in onset of activity or decreased absorption in patients with decreased peripheral perfusion, they noted no problems in their cohort. There is also anecdotal experience with the use of subcutaneous opioids in the PICU population [71, 281, 282]. Dietrich and Tobias retrospectively reviewed the subcutaneous administration of fentanyl in 24 PICU patients ranging in age from 2 weeks to 18 years [282]. The subcutaneous fentanyl infusions were administered for 1.5–14 days when intravenous administration was not feasible due to lack of intravenous access or drug incompatibilities. Opioids were given for the control of postoperative pain, as a gradual weaning regimen following prolonged opioid use, or for the provision of comfort during the terminal stages of a disease.

Although generally safe and effective, as with other agents, specific adverse effects on physiologic functions may occur with opioids. Although these agents may affect cardiovascular and ventilatory function like many of the previously described agents, an effect specific to the opioids is their potential impact on immune function. This effect of opioids and its mechanism remains poorly elucidated. Opioid receptors have been found on immune cells that participate in the inflammatory response. Binding of opioids to these receptors decreases inflammation and may play some role in the control of acute pain by opioids. However, in specific circumstances, this effect may be deleterious. Increased viral loads have been noted in patients with HIV infections who are receiving methadone [283]. Opioids have also been shown to modulate cytokine production and in an animal model, morphine administration led to reduced reticuloendothelial cell function, phagocytic count, phagocytic index, killing properties, and superoxide anion production [284, 285]. Further studies are needed to further define these effects, their mechanisms, and most importantly their effect on the overall immune health of the PICU patient.

Phenothiazines and Butyrophenones

The phenothiazines and butyrophenones are considered the "major tranquilizers". Their major clinical use is in the treatment of psychiatric disturbances or for their anti-emetic properties. Of the several agents available, haloperidol is the agent that is chosen most frequently for the sedation of adult patients in the ICU setting. Haloperidol acts through central dopamine receptors. With intravenous administration, its onset of action is within 10–20 min with a duration of action of 12–24 h, given its long elimination half-life of 18–26 h [286]. Although not approved by the United States' FDA for intravenous administration, there is significant clinical experience with its use by this route [287]. Although not routinely used in the PICU setting, this class of agent still sees frequent use for the control of delirium and psychosis in the adult ICU population. Despite the limited number of studies in the adult literature regarding the use of haloperidol for ICU sedation, significant findings have included a decreased incidence of withdrawal with higher cumulative doses of haloperidol and even decreased mortality in patients receiving haloperidol [288–290]. Milbrandt et al. conducted a retrospective review of 989 patients who required mechanical ventilation for more than 48 h and compared outcomes between patients who received haloperidol early on (within 48 h of the initiation of mechanical ventilation) and those who did not [290]. Patients who received haloperidol had lower in-hospital mortality (20.5 % versus 36.1 %, $p = 0.004$). These differences persisted even when adjusted for age, comorbid features, severity of illness, degree of organ dysfunction, and admitting diagnosis. Because of the retrospective nature of the study and the potential risks associated with haloperidol use (see below), the authors suggested that prospective, randomized trials were needed before applying this therapy routinely to all ICU patients.

There is only one report outlining the use of haloperidol in the PICU setting [291]. Haloperidol was administered by intermittent bolus dosing to five critically ill children, ranging in age from 9 months to 16 years, who were difficult to sedate despite escalating doses of benzodiazepines and opioids. Haloperidol was administered as a loading dose of 0.025–0.1 mg/kg. The loading dose was repeated every 10 min until the patient was sedated. The total loading dose required ranged from 0.09 to 0.25 mg/kg. This was followed by doses of 0.015–0.15 mg/kg (daily maintenance dose of 0.06–0.45 mg/kg/day) administered every 8 h. Haloperidol's efficacy was demonstrated by reductions of opioid/benzodiazepine requirements, decreased need for supplemental doses of sedative or neuromuscular blocking agents, and improved clinical sedation. One patient developed an oculogyric crisis (dystonic reaction), which resolved in 36 h without therapy. The haloperidol had already been discontinued in this patient.

Potential adverse effects associated with the butyrophenones and phenothiazines include hypotension related to peripheral α-adrenergic blockade with vasodilatation, dystonic and extrapyramidal effects, lowering of the seizure threshold, the neuroleptic malignant syndrome, and cardiac arrhythmias including *torsades de pointes* due to effects on repolarization. In the study by Riker et al. [289], one of the eight patients developed atrial dysrhythmias, prolongation of the QT interval, and ventricular tachycardia. The potential for cardiac dysrhythmias due to alterations in repolarization may be exacerbated in patients with altered sympathetic function related to fever, pain, or the stresses of an acute illness. Similar issues may occur with other drugs of this class including droperidol [292]. The US Food

and Drug Administration through a black box warning has focused on the potential association of droperidol and post-operative cardiac events including *torsades de pointes* in adult patients [293].

Alpha$_2$-Adrenergic Agonists

The physiologic effects of α_2-adrenergic agonists are mediated via stimulation of post-synaptic α_2-adrenoceptors that activate a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein), resulting in inhibitory feedback and decreased activity of adenylyl cyclase [294, 295]. The decreased intracellular concentration of cyclic adenosine monophosphate (cAMP) and decreased cAMP-dependent protein kinase activity results in the dephosphorylation of various species of ion channels, which modifies ion translocation and membrane conductance, resulting in decreased neuronal activation providing sedation and anxiolysis [296, 297]. The centrally acting α_2-adrenergic agonists also activate receptors in the medullary vasomotor center, thereby reducing norepinephrine turnover and decreasing central sympathetic outflow resulting in alterations in sympathetic function and decreased heart rate and blood pressure. Additional effects result from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus cereleus in the brainstem. The latter effect plays a prominent role in the sedation and anxiolysis produced by these agents, as decreased noradrenergic output from the locus cereleus allows for increased firing of inhibitory neurons, including the GABA system resulting in sedation and anxiolysis [298–300]. This effect is quite distinct from other agents commonly used for ICU sedation (benzodiazepines, barbiturates, propofol, and the volatile anesthetic agents). The EEG pattern and quality of sedation produced is similar to what occurs during non-REM sleep [300]. The lack of non-REM sleep with the prolonged use of other sedative agents is one of the physiologic factors that may lead to delirium during prolonged ICU stays. In the adult population, the presence of delirium has been linked to increased mortality especially in the elderly population. Aside from their sedative properties, the α_2-adrenergic agonists also provide some degree of analgesia or potentiation of opioid-induced analgesia through the regulation of substance P in the dorsal horn of the spinal cord.

Although initially introduced for the treatment of hypertension, the sedative, anxiolytic, and analgesic effects of clonidine have made it a useful agent as a premedicant for the operating room, to supplement caudal and epidural analgesia, as an adjunct to opioid-induced analgesia during the postoperative period, and for ICU sedation [301–306]. Although initially available only in tablet formulation, clonidine is now available both as a transdermal patch and as a preparation that is suitable for intravenous or neuraxial administration. Ambrose et al. evaluated the sedative and hemodynamic effects of a continuous clonidine infusion added to a midazolam infusion in a cohort of 20 PICU patients [305]. A continuous clonididne infusion at 1 μ/kg/h added to the midazolam infusion did not result in significant changes in heart rate, blood pressure or cardiac index. An increase in the infusion to 2 μg/kg/h was necessary in 2 of the 20 patients to provide adequate sedation. Arenas-Lopez et al. used enteral clonidine (3–5 μg/kg every 8 h) as an adjunct to intermittent doses of morphine and lorazepam for sedation during mechanical ventilation in 14 children [306]. Adequate sedation was achieved during 82 % of the study period with an overall decrease in the average hourly requirements for both lorazepam and morphine. No adverse effects were noted.

More recently, dexmedetomidine has been released for clinical use. Like clonidine, it is a centrally-acting, α_2-adrenergic agonist and exhibits the same physiologic effects. However, it possesses an affinity eight times that of clonidine for the α_2-adrenergic receptor, a differential α_1 to α_2 agonism of 1:1,600, and a half-life of 2 h, thereby allowing its titration by intravenous administration. Dexmedetomidine is currently approved by the United States FDA for two indications in adults including the short-term (24 h or less) sedation of adult patients during mechanical ventilation and for monitored anesthesia care. In healthy adult volunteers, the pharmacokinetic profile of dexmedetomidine includes a rapid distribution phase with a distribution half-life of approximately 6 min, an elimination half-life of 2 h, and a steady-state volume of distribution of approximately 1.33 l/kg [307]. Dexmedetomidine exhibits linear kinetics and is 94 % protein bound. Protein binding and plasma clearance are similar between adults and children, thus similar infusion rates may be used [308]. Children less than 2 years of age have a larger volume of distribution at steady state suggesting that a large loading dose may be needed [309]. Dexmedetomidine is extensively metabolized in the liver through glucuronide conjugation and biotransformation in the cytochrome P_{450} system. Hepatic clearance may be decreased by as much as 50 % in patients with severe hepatic dysfunction. Although renal impairment does not seem to alter pharmacokinetics, a potentiation of its effect may occur in patients with severe renal disease related to decreased protein binding and an increased free fraction of the drug [310].

Clinical trials in adult ICU patients have demonstrated the efficacy of dexmedetomidine in the provision of sedation during mechanical ventilation [307, 311, 312]. When compared with placebo in 119 adult patients who required mechanical ventilation following cardiac and general surgical procedures, patients receiving dexmedetomidine required 80 % less midazolam and 50 % less morphine [307]. Riker et al. compared dexmedetomidine

(0.2–1.4 μg/kg/h) to midazolam (0.02–0.1 mg/kg/h) in 375 medical/surgical adult ICU patients that required sedation for mechanical ventilation [311]. There was no difference in the time spent at the targeted RASS scores; however, there was a decrease in the prevalence of delirium (54 % versus 76.6 %) and a decrease in the time to tracheal extubation (3.7 days versus 5.6 days) in the patients that received dexmedetomidine. Although the patients treated with dexmedetomidine were more likely to develop bradycardia, they also had a lower likelihood of tachycardia or hypertension requiring treatment.

There are fewer prospective trials evaluating dexmedetomidine in pediatric-aged patients. In a prospective trial of infants and children requiring mechanical ventilation for respiratory failure, dexmedetomidine at a dose of 0.25 μg/kg/h was equivalent to midazolam at 0.22 mg/kg/h, while a dose of 0.5 μg/kg/h of dexmedetomidine was more effective than midazolam [313]. The efficacy of dexmedetomidine was demonstrated by a decreased need for supplemental morphine, as well as a decrease in the number of Ramsay scores of 1 exhibited by the patients. Dexmedetomidine was less effective in patients less than 6–12 months of age given that five of the six patients who exhibited a Ramsay score of 1 during dexmedetomidine use were less than 12 months of age. Various other investigators have demonstrated the efficacy of dexmedetomidine in various sedation scenarios in the PICU setting. However, the majority of these have been retrospective with a limited number of head-to-heard comparison with commonly used agents [314–316]. Of not is that there have been episodes of bradycardia in specific patients enrolled in these studies. During the postoperative period following cardiac surgery, this may result in the need for use of epicardial pacing. Although dexmedetomidine was more effective than their usual regimen with less depression of ventilator function, Hosokawa et al. noted that the frequency of bradycardia or hypotension was significantly higher in the dexmedetomidine group (21.4 % compared to 8.2 % in the usual sedation group) [314]. This required intervention in 5.3 % of patients.

Despite its efficacy, dexmedetomidine can have deleterious effects on ventilatory and cardiovascular function. The current literature regarding its effects on respiratory function is somewhat divergent depending on the dose administered and the method of assessing ventilatory function. Hall et al. noted no clinically significant change in $ETCO_2$, oxygen saturation, and respiratory rate with the administration of a bolus dose of dexmedetomidine (0.6 μg/kg) followed by an infusion (0.2–0.6 μg/kg/h), whereas Belleville et al. noted a depression of the slope of the CO_2 response curve and a decrease in minute ventilation at an $ETCO_2$ of 55 mmHg following a bolus dose of 2 μg/kg [317, 318]. Belleville et al. also noted irregular breathing patterns and short periods of obstructive apnea in some of the patients [318].

Adverse hemodynamic effects including hypotension and bradycardia effects have also been reported. Many of these events occur with the use of higher doses or during bolus dosing [319, 320]. Peden et al. reported that two patients in their study who received dexmedetomidine experienced brief episodes of sinus arrest following laryngoscopy and propofol administration [319]. These findings suggest that specific procedures (laryngoscopy), clinical scenarios (hypothermia) or medications (propofol, fentanyl, digoxin) may potentiate the vagotonic effects of dexmedetomidine. However, in specific clinical scenarios, the negative chronotropic and sympatholytic effects may be beneficial. In a cohort of 41 adult patients during vascular surgery, there was less tachycardia and decreased norepinephrine levels during emergence from anesthesia in patients receiving dexmedetomidine [320]. Other investigators have used the negative chronotropic effects as a therapeutic maneuver to treat arrhythmias following surgery for congenital heart disease [321].

The clinical experience with the use of the α_2-adrenergic agonist, dexmedetomidine, for sedation of the pediatric population continues to increase. Aside from its beneficial sedative properties, additional beneficial end-organ effects have been reported. Preliminary data in animal and human studies demonstrate beneficial effects on cerebral dynamics including a decrease in cerebral blood flow, $CMRO_2$, and ICP [322–324]. However, given the potential effects on mean arterial pressure, decreases in CPP may occur. Like the barbiturates, propofol, and the inhalational anesthetic agents, animal data suggest that dexmedetomidine may provide some degree of cerebral protection during periods of global or regional cerebral ischemia [325–327]. The data in animals regarding its effects on the seizure threshold are mixed depending on the provocative agent and the type of animal studied with two studies suggesting a lowering of the seizure threshold and two studies suggesting an anticonvulsant effect [328–331].

Ongoing experience suggests that dexmedetomidine may be an effective agent for sedation during non-painful procedures such as MR or CT imaging, either as a primary agent or as a rescue agent when other agents fail. Its limited effects on ventilatory function may be particularly efficacious especially when comparing it to other commonly used agents such as propofol. Koroglu et al. randomized 80 children (1–7 years of age) to dexmedetomidine or midazolam during MR imaging [332]. Dexmedetomidine was administered as a loading dose of 1 μg/kg over 10 min followed by an infusion of 0.5 μg/kg/h while midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 μg/kg/h. The quality of sedation was better and the need for rescue sedation was less (8 of 40 versus 32 of 40) with dexmedetomidine compared to midazolam. Similar efficacy was reported in an open label trial of dexmedetomidine for

sedation during MR imaging in 48 pediatric patients ranging in age from 5 months to 16 years who had failed sedation with alternative agents [333]. A second study by Koroglu et al. randomized 60 children to dexmedetomidine or propofol during MR imaging [334]. Although both of the agents were equally effective in providing sedation, propofol provided shorter induction times, recovery times, and discharge times. However, adverse effects including hypotension and oxygen desaturation were more common with propofol. Oxygen desaturation requiring intervention including a chin lift, discontinuation of the infusion or supplemental oxygen occurred in 4 of 30 children receiving propofol versus 0 of 30 receiving dexmedetomidine. Given its limited analgesic effects, dexmedetomidine may not to be the ideal agent when used alone for painful procedures. However, anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be effective in such scenarios [335]. In addition to having opposite effects on HR and BP, dexmedetomidine has been shown to blunt emergence phenomena from ketamine [336].

Chloral Hydrate

Chloral hydrate was first synthesized in 1832 and remains a popular for procedural sedation [337]. Its ongoing popularity may relate to its ease of administration by either the oral or rectal route, healthcare provider's experience and familiarity with it, and misconceptions regarding its margin of safety. Following oral or rectal administration, it is rapidly absorbed with a high bioavailability. It undergoes hepatic metabolism to trichloroethanol (TCE), its active component. Although generally effective for non-painful radiologic procedures, repeated dosing in the ICU setting can lead to excessive and prolonged CNS depression due to a variable half-life ranging from 9 to 40 h, as well as the accumulation of active metabolites [338]. These issues have resulted in recommendations of caution against its repetitive dosing from the American Academy of Pediatrics [339].

In addition to these concerns, like all of the sedative/analgesic agents that have been discussed in this chapter, respiratory and cardiovascular depression may occur with chloral hydrate. Despite the misconception that this agent is devoid of such adverse effects, apnea can occur with chloral hydrate and appropriate monitoring should always be used [340].

Chloral hydrate is relatively contraindicated in neonates given its competition with bilirubin for protein binding sites. Additionally, the active metabolite, trichloroethanol, is related to the halogenated hydrocarbons and may cause ventricular arrhythmias especially in patients at risk for such problems (tricyclic antidepressant ingestions) [341, 342]. Given these issues, chloral hydrate has a limited role in sedation in the PICU setting.

Conclusions

Due to the wide array of patients, ages, and clinical scenarios in the PICU population, a cookbook approach to sedation and analgesia is neither feasible nor desirable. As no single agent will be effective in all patients and all scenarios, those who provide care in this environment must be facile with the use of a wide array of sedative and analgesic agents. Furthermore, knowledge of the pharmacokinetics of these agents and their adverse effect profile is needed. In most scenarios, sedation is initiated with either a benzodiazepine or an opioid. There is an abundance of clinical experience with midazolam in the PICU population, although lorazepam may provide an effective alternative with a longer half-life and more predictable pharmacokinetics without the concern of active metabolites. However, there are limited reports regarding its use in the PICU population and with high dose infusions or its use in neonates and infants, there may be concerns regarding the diluent, propylene glycol. Although fentanyl is frequently chosen because of its lack of hemodynamic effects, morphine is an effective alternative. Preliminary data suggest that the development of tolerance may be slower and that there may be fewer issues with withdrawal than with fentanyl. Morphine's safety in the neonatal population has been evaluated and long-term follow-up studies have demonstrated no adverse CNS developmental effects from its use in neonates and infants.

When the above agents fail or lead to adverse effects, alternatives include ketamine, pentobarbital, or dexmedetomidine. Ketamine may be useful for the patient with hemodynamic instability or with increased airway reactivity as a component of their disease process. To date, there are limited reports regarding the use of pentobarbital in the PICU with recent concerns being raised regarding a high incidence of adverse effects associated with its use. Propofol has gained great favor in the adult population as a means of providing deep sedation while allowing for rapid awakening. Similar beneficial properties are achieved in the pediatric-aged patient; however, its use is not recommended given its association with the "propofol infusion syndrome". As the pediatric experience increases, it appears that there will be a role for newer agents such as dexmedetomidine. Suggested starting guidelines for sedative and analgesic agents are listed in Table 3.5.

Regardless of the scenario and agent chosen, adverse effects on physiologic function may occur with the use of sedative and analgesic agents. Therefore, close monitoring of a patient's physiologic function is mandatory when sedative and analgesia is provided. There is also an increased understanding and recognition of withdrawal syndromes which may occur following the prolonged administration of sedative and analgesic agents. Strategies should be implemented to identify those patients at risk for withdrawal with appropriate interventions to prevent

Table 3.5 Suggested guidelines for dosing of sedative and analgesic agents

Agent	Dose	Comments
Fentanyl	2–3 μg/kg/h	Modulates stress response and pulmonary vascular resistance
Remifentanil	0.1–0.3 μg/kg/min	Short-half due to esterase metabolism, rapid development of tolerance, cost issues
Morphine	10–30 μg/kg/h	Inexpensive, venodilation, delayed onset of tolerance compared to fentanyl
Midazolam	0.05–0.15 mg/kg/h	Abundant clinical experience, P_{450} metabolism
Lorazepam	0.025–0.05 mg/kg/h	Limited clinical experience, inexpensive, metabolism: glucuronyl transferase, potential issue with propylene glycol
Ketamine	1–2 mg/kg/h	Endogenous catecholamine release, bronchodilation, cardiovascular stability
Pentobarbital	1–2 mg/kg/h	Incompatible with other medications, vasodilation/negative inotropic effects
Propofol	1–3 mg/kg/h	Rapid awakening, high lipid content of solution, not recommended due to potential association with propofol infusion syndrome
Haloperidol	0.06–0.45 mg/kg/day	Limited clinical experience, potential for cardiac arrhythmias
Dexmedetomidine	0.25–0.75 μg/kg/h	FDA approved for short term (24 h) sedation in adults; limited clinical data in pediatric population

The infusion rates are suggestions for starting doses. The actual infusion rate should be titrated up or down based on the patient's actual requirements

its occurrence. These may include a gradual tapering of the infusion rate or switching to oral or subcutaneous administration. As this is an increasing problem in the PICU setting, newer strategies to prevent its occurrence such as the use of NMDA antagonists or rotating sedation regimens warrant further investigations. With such caveats in mind, we can continue to strive to provide effective sedation and analgesia for all of our patients.

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Tolerance, Physical Dependency, and Withdrawal

4

Joseph D. Tobias

Abstract

As clinicians in the Pediatric ICU, we have become increasingly aware of the potential adverse effects related to inadequate sedation and poor pain control. These concerns combined with ongoing humanitarian needs to provide appropriate sedation and analgesia during critical illness have led to the increased use of sedative and analgesic agents. These initiatives have also led to new consequences that must be addressed including physical dependency, tolerance, and withdrawal. Strategies are needed to identify those patients at risk for withdrawal followed by appropriate interventions to prevent or treat it. These may include a gradual tapering of the infusion rate or switching to oral or subcutaneous administration. As this is an increasing problem in the PICU setting, newer strategies to prevent its occurrence such as the use of NMDA antagonists or rotating sedation regimens warrant further investigations. With these caveats in mind, the goal of providing effective and safe sedation and analgesia for all of our patients is within reach.

Keywords

Withdrawal • Tolerance • Physical dependency • Methadone • Opioids • Benzodiazepines

Introduction

As clinicians in the Pediatric Intensive Care Unit (PICU), we have become increasingly aware of the potential adverse effects related to inadequate sedation and poor pain control. Clinical investigations have demonstrated significant deleterious physiologic effects of untreated pain [1–3]. These concerns combined with ongoing humanitarian needs to provide appropriate sedation and analgesia during critical illness have led to the increased use of sedative and analgesic agents. Despite the benefits of such care, these initiatives have also led to new consequences that must be addressed including physical dependency, tolerance, and withdrawal. As our understanding of these processes increases, it is evident that these concerns require definition and effective prevention and treatment strategies.

Tolerance, Physical Dependency and Withdrawal

An appropriate place to begin the development of an effective approach to the patient with tolerance and physical dependency is a consensus on definitions of these terms (Table 4.1) [4, 5]. Tolerance is a decrease in a drug's effect over time or their requirement of dose escalations to achieve the same level of sedation or analgesia. Tolerance is related to changes at or distal to the receptor, generally at the cellular level (see below). Tolerance can be divided into subcategories: (1) *innate tolerance* – a genetically predetermined lack of sensitivity to a drug, (2) *pharmacokinetic or dispositional tolerance* – changes in a drug's effect because of alterations in its distribution or metabolism, (3) *learned tolerance* – a reduction in a drug's effect related to learned or

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Table 4.1 Definitions

Tolerance	A decrease in a drug's effect over time or the need to increase the dose to achieve the same effect. Tolerance is related to changes at or distal to the receptor, generally at the cellular level
Withdrawal	The physical signs and symptoms that manifest when the administration of a sedative or analgesic agent is abruptly discontinued or pharmacologically reversed in a patient who is physically tolerant
Physical dependency	The physiological or biochemical adaptions which occur and require the continued administration of a sedative or analgesic agent to prevent the clinical signs of withdrawal
Psychological dependency	The need for a substance because of its euphoric effects
Addiction	A complex pattern of behaviors characterized by the repetitive, compulsive use of a substance related to psychological dependence or cravings due to the euphoric or psychedelic effects of a drug. Frequently associated with antisocial or criminal behavior to obtain the drug, and a high incidence of relapse after treatment
Tachyphylaxis	Rapid loss of a drug's effect caused by compensatory physiologic or biochemical mechanisms frequently related to exhaustion of neurotransmitters, activation of antagonistic systems, or enzyme changes

compensatory mechanisms (learning to walk a straight line while intoxicated by repeated practice), and (4) *pharmacodynamic tolerance* [3–5] With pharmacodynamic tolerance, although the plasma concentration of the drug remains constant, there is a decreased effect. For the purpose of this discussion the terms tolerance and pharmacodynamics tolerance will be considered synonymous as the other issues are not as relevant when considering the PICU patient. Withdrawal refers to the clinical signs and symptoms that occur when a sedative or analgesic agent is abruptly discontinued or pharmacologically reversed in a tolerant patient. The symptomatology of withdrawal varies significantly, being affected by several factors including the agent that has been administered and patient factors such as age, cognitive state, associated medical conditions and co-morbid states. When discussing dependency, a distinction must be made between physiologic dependency (otherwise known as physical dependency) and psychological dependency (Table 4.1). Addiction is a complex pattern of behaviors characterized by the repetitive, compulsive use of a substance, frequently associated with antisocial or criminal behavior to obtain the drug, and the continued use of the drug despite its harmful physiologic effects. With addiction, there is a high probability of relapse after treatment. Psychological dependency and addiction are extremely rare after the appropriate use of sedative or analgesic agents to treat pain or to relieve anxiety in the PICU setting.

History

Recognition of the problems of opioid dependency and withdrawal were first encountered in the 1970s and 1980s in infants of drug-addicted mothers [6, 7]. Although the origin of the problem was different, these reports provided valuable information on which some strategies were built for dealing with similar problems in the PICU. The reports from the 1970s and 1980 have provided starting points for both pharmacologic treatment regimens as well as scoring systems. The latter were initially used to grade the severity of withdrawal and then later to evaluate the efficacy of the treatment regimens.

Reports of dependency and withdrawal in the PICU initially involved opioids and were centered around the most critically ill patients, including children requiring extracorporeal membrane oxygenation (ECMO) as well as infants who required prolonged courses of mechanical ventilation following surgery for congenital heart disease [8–10]. In a retrospective review that included a cohort of 37 neonates who were sedated with fentanyl during ECMO for respiratory failure, Arnold et al. sought to identify the signs and symptoms of the neonatal abstinence syndrome (NAS) and the risk factors for its occurrence [8]. The investigators noted that the fentanyl infusion requirements to achieve the desired level of sedation increased from 11.6 ± 6.9 μg/kg/h on day 1 to 52.5 ± 19.4 μg/kg/h on day 8. The increased infusion requirements correlated with an increase in the plasma fentanyl concentration, thereby demonstrating pharmacodynamic and not pharmacokinetic tolerance. The incidence of NAS correlated with both the total fentanyl dose and the duration of the infusion, but not the peak infusion rate. Risk factors for NAS included a cumulative fentanyl dose ≥1.6 mg/kg or an ECMO duration (fentanyl infusion duration) ≥5 days (odds ratio of 7 and 13.9, respectively). In that same year, the first protocol using oral methadone for opioid withdrawal after the prolonged administration of fentanyl in the PICU was published [10]. Although the report focused on the use of oral methadone, the three infants reported demonstrated the problem of opioid tolerance, dependency, and withdrawal in a PICU population that was older and who had different medical/surgical problems (post cardiac surgery patients) from those reported by Arnold et al. Subsequent reports demonstrated withdrawal from other agents used for prolonged sedation in the PICU, including benzodiazepines, barbiturates, propofol, dexmedetomdine, chloral hydrate, and even the inhalational anesthetic agents (Table 4.2) [11–26].

Mechanisms of Tolerance

When considering the mechanisms of tolerance, there has been considerable investigation and subsequent information acquired regarding opioid therapy, including mechanisms of

Table 4.2 Tolerance, physical dependency and withdrawal from sedative and analgesic agents

Authors and reference	Agent	Description and key findings
Arnold et al. [8]	Fentanyl	Initial report in ECMO population. Risk factors identified including total fentanyl dose ≥1.5 mg/kg and ECMO duration ≥5 days
Arnold et al. [9]	Fentanyl	Fentanyl infusion requirements increased from 9.2 ± 1.9 μg/kg/h on day 1 to 21.9 ± 4.5 μg/kg/h on day 6. As in their previous study, they are noted an increase in the plasma fentanyl concentration from 3.1 ± 1.1 ng/mL on day 1 to 13.9 ± 3.2 ng/mL on day 6
Tobias et al. [10]	Fentanyl	Anecdotal report of the use of fentanyl to treat withdrawal in 3 infants following surgery for congenital heart disease
Sury et al. [11]	Midazolam	Anecdotal report of 3 children with after prolonged sedation with a continuous infusion of midazolam for 7, 14, and 17 days at mean infusion rates of 0.17, 0.22, and 0.56 mg/kg/h. The infusions were stopped without tapering the infusion rate. Withdrawal symptoms included visual hallucinations, combative behavior, and seizures
van Engelen et al. [12]	Midazolam	Two pediatric patients. Withdrawal after midazolam infusions of 12 and 29 days. Symptoms included agitation, tachycardia, hyperpyrexia, and vomiting
Fonsmark et al. [13]	Midazolam and pentobarbital	Series of 40 children who received sedation with midazolam, pentobarbital, or a combination of the two. Withdrawal occurred in 14 of 40 patients (35 %). Risk factors included a cumulative midazolam dose ≥60 mg/kg or a cumulative pentobarbital dose ≥25 mg/kg
Tobias et al. [14]	Pentobarbital	Pentobarbital withdrawal following prolonged sedation in a 17-month-old child
Imray et al. [17]	Propofol	Propofol withdrawal in a 10-month-old girl who required mechanical ventilatory support for 2 weeks. When the propofol was discontinued, the patient exhibited "generalized twitching and jitteriness"
Arnold et al. [20]	Volatile anesthetic agents (isoflurane)	Withdrawal in 5 of 10 pediatric patients who received isoflurane for sedation during mechanical ventilation. These five patients had received more than 70 MAC-hours
Honey et al. [25]	Dexmedetomidine	Neurologic issues were noted in 4 of 36 patients following dexmedetomidine infusions. Adverse events were more likely when the cumulative dose was ≥8.5 μg/kg
Da Silva et al. [26]	Chloral hydrate	33-month-old with 40 days of chloral hydrate sedation (daily dose of 120–200 mg/kg/day). Withdrawal treated with clonidine

action, hyperalgesia and tolerance [5, 27]. Although there remains a paucity of data regarding the mechanisms responsible for withdrawal from other sedative agents, many of the intracellular mechanisms and physiologic processes may share similarities with the opioids [4]. Tolerance results primarily from two mechanisms: (1) receptor desensitization and (2) the upregulation of the cAMP pathway [28, 29]. Other mechanisms that may play a role include neuroimmune activation, the production of antiopioid peptides, and the spinal dynorphin system [4, 27]. Several mechanisms have been proposed to explain receptor desensitization (Table 4.3) [30–35]. Likewise, there are varied proposed mechanisms responsible for the upregulation of the cAMP pathway (Table 4.4) [28, 29, 36–38]. Many of these effects and those that lead to the intracellular changes that result in tolerance are the result of neuronal protein kinases including secondary messenger dependent protein kinases such as calcium/calmodulin-dependent protein kinase II or protein kinase A and G protein–coupled receptor kinases (GRKs). Activation of the protein-kinase systems phosphorylates opioid receptors resulting in altered function of the ion channels. Regulation of the induction and function of the protein-kinase systems is dependent on the interactions of the opioid receptors and non-opioid excitatory systems including glutamate and the NMDA system, γ-amino butyric acid (GABA) A, and the α_2-adrenergic system.

Table 4.3 Mechanisms of receptor desensitization

1. Down-regulation of opioid receptors [30]
2. Receptor internalization mediated via the β-arrestin system [31, 32]
3. Opioid receptor uncoupling from inhibitory G proteins (G_i) [33]
4. Increased cytoplasmic nitric oxide via induction of nitric oxide synthetase [34]
5. Altered activity of non-G_i proteins [35]

Table 4.4 Mechanisms involved in the upregulation of the cAMP pathway

1. Increased activity of adenylate cyclase supersensitization of AC [29]
2. Opioid receptor coupling and interactions with Gs proteins [36]
3. Upregulation of spinal glucocorticoid receptors [28, 37, 38]
(a) Mediated through cAMP response element-binding (CREB) protein–dependent pathway with activation of protein kinase Cγ (PKCγ) and alteration of the N-methyl-d-aspartate (NMDA) pathway

Clinical Signs and Symptoms of Withdrawal

The first step in the development of strategies to provide treatment of tolerance and related problems is a means to allow the accurate identification and recognition of the problem. Scoring systems may be helpful in the management of patients presenting with signs and symptoms of withdrawal,

Table 4.5 Signs and symptoms of withdrawal

1. CNS manifestations
(a) Increased irritability
(b) Decreased sleep
(c) Inability to concentrate
(d) Tremulousness
(e) Hyperactive deep tendon reflexes
(f) Clonus
(g) Frequent yawning
(h) Sneezing
(i) Delirium
(j) Hypertonicity
(k) High-pitched cry
(l) Exaggerated Moro reflex
(m) Seizures
(n) Visual and auditory hallucinations
2. GI manifestations
(a) Emesis
(b) Diarrhea
(c) Feeding intolerance
3. Activation of the sympathetic nervous system
(a) Tachycardia
(b) Hypertension
(c) Dilated pupils
(d) Tachypnea
(e) Nasal stuffiness
(f) Sweating
(g) Fever

Table 4.6 Sedation Withdrawal Score (SWS) designed by Cunliffe M

1. Central nervous system
(a) Tremor
(b) Irritability
(c) Hypertonicity
(d) High pitched cry
(e) Convulsions
(f) Hyperactivity
2. Gastrointestinal system
(a) Vomiting
(b) Diarrhea
3. Autonomic nervous system
(a) Fever
(b) Sweating
(c) Sneezing
(d) Respiratory rate

Based on data from Cunliffe et al. [40]

not only in identifying the behaviors or withdrawal, but also in grading its severity and judging the response to therapy. Regardless of the scoring system that is used, the clinical signs and symptoms are generally confined to the CNS, the gastrointestinal tract, and the sympathetic nervous system (Table 4.5). Of note is the overlap between the signs and symptoms of withdrawal and other serious illnesses that may arise in the PICU setting, including sepsis, psychosis, delirium, necrotizing enterocolitis, and altered cerebral perfusion. These and other conditions which can manifest similar clinical signs and symptoms must be investigated and ruled out before concluding that the patient's symptoms are the result of withdrawal. Although many of the signs and symptoms of withdrawal are the same regardless of the agent, there may be subtle differences depending on the specific agent. The time to the onset of withdrawal symptoms varies depending on the half-life of the agent and the half-life of active metabolites, which may be several times longer than the parent compound.

Initially, care of patients with withdrawal relied on the use of scoring systems such as the Finnegan score that were developed for neonates born to drug-addicted mothers. However, it soon became apparent that such systems were not applicable to the older PICU population [27]. These concerns were echoed by Ista et al. in their review of the withdrawal scoring systems applicable to the PICU patient [39]. They noted that only two were directed toward the PICU population. The first of these was the Sedation Withdrawal Score (SWS) which assigned 0–2 points for 12 different withdrawal behaviors thereby resulting in a maximum score of 24 (Table 4.6) [40]. The authors recommended using the system to grade the severity of withdrawal as well as a means to decide on weaning the current regimen (0–6 wean, 6–12 no change, 12–18 revert to previous regimen, more than 18 re-evaluate plan). However, Ista et al. noted that the scale had not been validated in children and that there are no data regarding its sensitivity, specificity, validity, and reliability. The second scale identified in the review by Ista et al. was the Opioid and Benzodiazepine Withdrawal Scale (OBWS) developed by Franck et al., which uses a 21 item checklist that evaluates 16 specific withdrawal behaviors (Table 4.7) [41]. A score ≥8 is considered indicative of withdrawal. An evaluation of the OBWS using 693 assessments in 15 children, varying in age from 6 weeks to 28 month, demonstrated a sensitivity of only 50 % with a specificity of 87 %. The predictive value in terms of positive and negative ratios was 4.0 and 0.57 (considered moderate for a diagnostic tool) while the inter-rater reliability was acceptable at 0.8.

Because of these issues, Ista et al. noted that a better scale was necessary in the PICU population. Using data from their previous review, they developed their own withdrawal scale [42]. The scale included all of the behaviors in the literature reported as manifestations of withdrawal in the pediatric-aged patient. From this, they developed the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC) which included 24 withdrawal symptoms (Table 4.8) [42]. Over a 6 month period, 2,188 individual observations were collected in 79 children within 24 h of discontinuing sedative and/or analgesic medication. They noted that specific symptoms including

Table 4.7 Opioid and Benzodiazepine Withdrawal Scale (OBWS)

1. Central nervous system
(a) Crying or agitation
(b) Sleeplessness
(c) Movement disorder
(d) Hallucinations
(e) Exaggerated Moro
2. Gastrointestinal system
(a) Vomiting
(b) Diarrhea
3. Autonomic nervous system
(a) Temperature instability
(b) Respiratory rate
(c) Diaphoresis
(d) Sneezing
(e) Dilated pupils
(f) Yawning
4. Miscellaneous
(a) Nasal congestion or stuffiness
(b) Frequent need for suctioning

Reprinted from Franck et al. [43]. With permission from Elsevier

agitation, anxiety, muscle tension, sleeping for less than 1 h, diarrhea, fever, sweating, and tachypnea were observed most frequently. Twenty-three observations were scored simultaneously and resulted in an inter-observer correlation coefficient of 0.85 with a range of 0.59–1.0 for the individual items. However, they did not come up with a specific scoring system. In fact, they concluded that the SBOWC could form the basis for an assessment tool for withdrawal symptoms in the PICU patient. However, they did not think that all of the items in the SBOWC were clinically relevant. Additionally, they suggested that in a further study, it would be advisable to have independent observers assess videotaped material, so as to increase the validity and reliability. Also, they noted that items on the checklist should be further clarified so to ensure there is no misinterpretation possible for nurses and that item reduction is needed to achieve easier clinical use.

One final tool (WAT-1) was introduced to the literature in 2008 by Franck et al. (Table 4.9) [43]. The tool built on their previous work and that of others. Most importantly, they provide a simple tool with 11 scoring points, ten of which provide a yes (1 point) or no (0 points) system. The final evaluation point is the time to gain a calm state when agitated. It gives a score of 0 for less than 2 min, a score of 1 for 2–5 min, and a score of 2 if more than 5 min are required. Their initial study included a total of 1,040 assessments in 83 pediatric patients with a median age of 35 months, who were recovering from acute respiratory failure and were weaning from more than 5 days of a continuous infusion or round-the-clock administration of opioids and benzodiazepines. Generalized linear modeling was used to analyze each

Table 4.8 Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC)

1. Central nervous system
(a) Agitation
(b) Anxiety
(c) Increased muscle tone
(d) Motor disturbances
(i) Slight muscle jerks
(ii) Uncoordinated, robust movements
(e) Tremors
(i) Spontaneous
(ii) In response to stimulation
(f) Inconsolable crying
(g) High pitched cry
(h) Sleep time
(i) Less than 1 h
(ii) More than 1 h and less than 3 h
(i) Seizures
(j) Pupillary dilatation
(k) Hallucinations
2. Gastrointestinal system
(a) Vomiting
(b) Diarrhea
(c) Increased residuals after feedings
(d) Poor feeding
3. Autonomic nervous system
(a) Tachycardia
(b) Tachypnea
(c) Hypertension
(d) Fever
(e) Sweating
(f) Sneezing
(g) Yawning
(h) Mottling

Based on data from Ista et al. [42]

Table 4.9 Withdrawal assessment tool 1 (WAT-1)

1. Loose or watery stools
2. Vomiting, retching, gagging
3. Temperature ≥37.8 °C
4. State: awake and distressed or awake and calm
5. Tremor
6. Sweating
7. Uncoordinated, repetitive movement
8. Yawning or sneezing
9. Startle to touch
10. Increased muscle tone
11. Time to gain calm state
(a) Less than 2 min (0)
(b) 2–5 min (1)
(c) More than 5 min (2)

Reprinted from Franck et al. [43]. With permission from Lippincott Williams & Wilkins

symptom in relation to withdrawal intensity ratings. Symptoms with high redundancy or low levels of association with withdrawal intensity ratings were dropped resulting in the 11-item (12-point) scale. Concurrent validity was indicated by high sensitivity (0.872) and specificity (0.880) with a WAT-1 ≥3 predicting withdrawal.

Prevention of Tolerance

As with many problems, the effective treatment of withdrawal should focus on prevention. Regardless of the agent, the data demonstrate that the incidence of withdrawal is related to not only the duration of administration, but also the total dose of the medication delivered. As such, achieving effective sedation with the least amount of medication remains the goal. To achieve this, ongoing assessment of the depth of sedation at regular intervals is suggested. During the management of pain in the inpatient setting, there has been great success with the idea that pain assessment is the fifth vital sign. Perhaps a similar process should occur in the PICU setting where assessment of sedation is considered the fifth vital sign so that a score is applied every time the other vital signs are measured. This not only ensures that patients are adequately sedated, but should also help in identifying those with excessive sedation. In the latter group, a decrease in the amount of sedation is indicated.

The various clinical sedation scales have been reviewed elsewhere in this textbook in the chapter outlining sedation in the PICU patient [44–48]. The most commonly used PICU sedation scores evaluate physiologic variables, an objective assessment of the patient's depth of sedation, or a combination of the two. There are several scales which have been validated in the pediatric patient including those who are tracheally intubated and receiving mechanical ventilation. Given issues with clinical sedation scales and their limited utility in critically ill patients or those receiving neuromuscular blocking agents, other methods to judge the depth of sedation may be required. In the operating room setting during the provision of anesthesia, there is growing interest in the use of "depth of anesthesia monitors". In general, these monitors use a preset algorithm to interrogate the processed EEG pattern and provide a numeric value ranging from 0 (isoelectric) to 100 (awake with eyes open). Of note, the EEG algorithms were developed predominantly during the use of agents that act through the GABA system including the volatile anesthetic agents, barbiturates, propofol, and benzodiazepines. As such, their utility is limited with the use of other agents such as opioids, etomidate or those that act through the NMDA system (ketamine, nitrous oxide). Although, there are now several of these "depth of anesthesia" monitors available, the first one introduced into clinical practice and the one that has seen the greatest use both in and out of the operating room is the Bispectral Index (BIS monitor, Aspect Medical, Newton, MA). To date, these monitors have seen the greatest use intraoperatively monitoring the effects of general anesthetic and sedative agents. Although a BIS value less than 60–70 has been shown to correlate with a low probability of intraoperative awareness, its superiority over other intraoperative monitors such as end-tidal gas monitor as a means of limiting awareness has not been proven [49–52]. Additional issues have been raised regarding the use of depth of anesthesia monitoring in the PICU setting including the inaccuracy of these devices with non-GABA agents as well as variations in the BIS number related to artifact from ICU devices and interference from the EMG of the frontalis muscle. Given these concerns, it is unlikely that such devices will see routine use for monitoring sedation in the PICU population. However, they may have some utility in situations where clinical scales cannot be used, such as during the administration of neuromuscular blocking agents. In a cohort of 12 PICU patients receiving NMBA's and sedation with either midazolam or propofol, BIS values were prospectively recorded [53]. Although the BIS number was recorded by a bedside computer every 10 s, the number was concealed from health care workers. BIS values were recorded for 476 h (161,893 BIS values) in 12 patients. The BIS number was 50–70, 57 % of the time; ≤49, 35 % of the time; and greater than 70, 8 % of the time. When supplemental doses of sedatives were administered, the BIS number was greater than 70, 64 % of the time; 50–70, 31 % of the time; and ≤49, 5 % of the time. Oversedation was more likely with propofol than midazolam. The authors concluded that during the use of neuromuscular blocking agents, physiologic parameters were an inadequate means of judging the depth of sedation, oversedation was a common occurrence and that supplemental doses of sedative agents are occasionally used despite the fact that the BIS would indicate an adequate depth of sedation.

To date, there are no data to suggest that there are effective clinical ways of delaying the onset of tolerance by the co-administration of other pharmacologic agents. Given the mechanisms of the development of tolerance, theoretical information and some animal data suggest that the co-administration of agents that are antagonists at the mu or delta opioid receptors, agonists at the kappa opioid receptor, or antagonists at the NMDA receptor can delay tolerance [54–59]. However, in clinical practice, none of these have clearly been shown to be effective and as such, none are in common clinical use. Darnell et al. have clearly demonstrated that a simple technique such as the coadministration of naloxone does not effectively delay the onset of tolerance [60]. A total of 82 children, varying in age from 1 day to 18 years, requiring mechanical ventilation and fentanyl infusions for more than 4 days were enrolled in a double-blinded, randomized, placebo-control trial. In addition to fentanyl infusions, patients received either a low-dose naloxone infusion (0.25 μg/kg/h) or placebo to evaluate the effects on fentanyl requirements during mechanical ventilation. When

comparing those treated with naloxone and those receiving placebo, there was no difference in the maximum cumulative daily fentanyl dose or the total fentanyl dose received throughout the study period (360 μg/kg versus 223 μg/kg). In fact, there was a trend toward fewer rescue midazolam boluses, lower total midazolam dose, and fewer rescue fentanyl boluses doses in the placebo-treated group.

Similarly, although ketamine may be used as an analgesic adjuvant in opioid tolerant patients, the clinical evidence does not support its role in delaying the onset of tolerance in the setting of acute pain [61–64]. Several case reports and series have outlined the efficacy of ketamine in providing analgesia in chronic pain patients who have become tolerant to opioids. However, in this scenario, the mechanism is likely non-opioid mechanisms involved in analgesia and not the provision of an acute reduction in opioid tolerance. When studied intraoperatively in patients receiving remifentanil as part of their anesthetic, no reduction in acute tolerance to remifentanil was demonstrated in patients receiving ketamine versus placebo [65]. Given these data, to date, there are is evidence-based medicine to support the co-administration of pharmacologic agents as a means of delaying the onset of tolerance.

In clinical practice, some simple maneuvers may be considered to limit the acute tolerance related to opioids. Tolerance to any sedative or analgesic agent is related to receptor occupancy time and the affinity with which the agonist binds to the receptor. When feasible, the intermittent administration of longer acting-agents may offer the advantage of delaying the onset of tolerance over the continuous infusion of short-acting agents. Given decreased affinity for the opioid receptor compared to the synthetic opioids, morphine may be considered in hemodynamically stable patients as a means of limiting the rapidity with which tolerance develops. In a cohort of infants requiring sedation and analgesia during ECMO for an average of 4–5 days), morphine provided equivalent levels of sedation while decreasing the need for supplemental bolus doses of opioid [66]. Additionally, infants receiving morphine had a lower incidence of withdrawal (13 of 27 with fentanyl versus 1 of 11 with morphine, $p<0.01$) and were hospitalized for fewer days after ECMO (31.1 ± 14 versus 21.5 ± 7.0 days, $p=0.01$).

Although preliminary studies demonstrate that remifentanil may be an effective agent, the development of tolerance is more rapid that with other synthetic opioids including fentanyl. This has translated into greater postoperative opioid requirements when remifentanil is used intraoperatively and the need to escalate doses rapidly when remifentanil is used for ICU sedation. This combined with its cost make it a relatively undesirable agent for most scenarios in the PICU patient [67, 68].

More recently, in the adult population the use of drug holidays has been suggested as a means of delaying or limiting tolerance [69]. In a randomized, controlled trial involving 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a medical intensive care unit, study patients had the sedative infusions interrupted on a daily basis until the patients were awake. In the control group, the infusions were interrupted only at the discretion of the clinicians in the intensive care unit. In the intervention group, there was a reduction in the duration of mechanical ventilation (median of 4.9 versus 7.3 days, $P=0.004$) and in the length of ICU (median of 6.4 versus 9.9 days, $P=0.02$). Six of the patients in the intervention group (9 %) required diagnostic testing to assess changes in mental status, as compared with 16 of the patients in the control group (27 %, $P=0.02$). No difference in the incidence of complications such as removal of the endotracheal tube by the patient was noted between the two groups. Although an increasing practice in the adult population, there are currently no data regarding drug holidays in the PICU setting. Given the accumulating data regarding the efficacy of this practice in adults, investigations in the pediatric population seem warranted. Although concerns have been expressed regarding potential adverse effects related to this practice such as excessive agitation in critically ill patients, the adult data support the safety of these practices.

Identification of the Group at Risk for Withdrawal

In order to provide effective therapy for patients with withdrawal, it may be helpful to identify those patients who have developed physical dependency and are therefore likely to manifest symptoms of withdrawal. In such patients, options to prevent withdrawal such as the slow weaning of opioid and sedative infusions or the switch to orally active agents should be considered. Regardless of the agent, the risk factors for physical tendency generally include the duration of the infusion and the total dose administered. No correlation has been noted with the maximum infusion rate. In a prospective trial of 23 infants and children who had received fentanyl infusions for sedation during mechanical ventilation, both the total fentanyl dose and the duration of the infusion correlated with the risk of withdrawal [70]. The incidence of withdrawal was 50 % when the total fentanyl dose was ≥1.5 mg/kg or when the duration of the infusion was ≥5 days. The incidence of withdrawal was 100 % with a total fentanyl dose ≥2.5 mg/kg or an infusion duration ≥9 days. With other sedative agents, the risk of withdrawal has also been shown to correlate with both the total dose administered as well as the duration of the infusion. In infants sedation with fentanyl during ECMO, the incidence of withdrawal correlated with both the total dose (more than 1.6 mg/kg) and the duration of administration (more than 5 days) of fentanyl [8]. The same investigators also reported that the total dose administered may be a risk factor for patients receiving sedation using the inhalation anesthetic

agent, isoflurane. Withdrawal occurred only in patients who had received more than 70 MAC-hours of isoflurane [19, 20]. Fonsmark et al. reported an increased probability of withdrawal in patients who received a total dose of midazolam ≥60 mg/kg or a total dose of pentobarbital ≥25 mg/kg [13]. More recently, the risk of withdrawal following the prolonged use of dexmedetomidine has also been shown to be greater when the total dose administered is ≥8.5 μg/kg or when the duration of the infusion is more than 5–7 days [25]. Additional risk factors noted in the adult population include an increased risk of withdrawal with the concomitant administration of neuromuscular blocking agents and a decreased risk of withdrawal with increased dosing of haloperidol [17].

Weaning Strategies and Treatment of Withdrawal

By identifying the high risk population and vigilant assessment with withdrawal scores developed for the PICU patient, it seems that we are closer to our goal of identifying patients who are manifesting withdrawal symptoms. The prevention of withdrawal starts with the identification of patients who are likely to be physically tolerant followed by slowly weaning the sedative and analgesic agents in these patients. Even with shorter durations of administration (3–4 days), withdrawal scales should still be applied to all PICU patients following the discontinuation of sedative and analgesic medications as withdrawal can still occur with shorter durations of therapy.

Based on limited evidence-based medicine, it has been suggested that that weaning can be accomplished at a rate of 10–20 % per day even in patients who had received 5–7 days of therapy [71, 72]. However, with these protocols, a significant incidence of withdrawal has been noted, thereby suggesting that a more reasonable approach may be a 5–10 % decrease per day [73, 74]. Although the weaning process can be accomplished by slowly decreasing the intravenous infusion rate, this mandates the maintenance of intravenous access, ongoing hospitalization, and at times, continued monitoring in the PICU. The latter will depend on local hospital policies and practices. However, many will mandate ongoing monitoring in and ICU setting when certain medications such as fentanyl or midazolam are administered by continuous infusion.

To facilitate transfer out of the PICU and in an effort to limit the need for ongoing intravenous access, options to consider include either switching to subcutaneous or oral administration. If gradual tapering the infusion can be accomplished within a reasonable period of time (5–10 days) that will not delay hospital discharge, switching to oral medications will generally not expedite discharge home. In this scenario, the use of subcutaneous infusions may be considered [75]. Although used mostly commonly for the treatment of chronic pain issues including those related to the terminal stages of oncologic diseases, there is increasing use of the subcutaneous route for the treatment of acute pain and anecdotal experience regarding its use in patients with physical tolerance following prolonged sedation in the PICU setting. These patients are generally receiving moderate doses of fentanyl (5–10 μg/kg/h) and/or midazolam (0.1–0.3 mg/kg/h). The switch to the subcutaneous route allows the removal of central venous access, eliminates the need to maintain peripheral intravenous access, and depending on individual hospital policies may eliminate the needing for ongoing care in the PICU setting. In a retrospective review of nine patients ranging in age from 3 to 7 years, the transition from intravenous fentanyl and/or midazolam to the subcutaneous route was accomplished without interruption in the infusion or the development of withdrawal [75]. The starting infusion rate for subcutaneous fentanyl varied from 5 to 9 μg/kg/h. Four patients had also received subcutaneous midazolam at a rate of 0.15–0.3 mg/kg/h. No problems with the subcutaneous access were noted during the 3–7 day treatment periods in the nine patients. The fentanyl infusion was decreased by 1 μg/kg/h every 12–24 h and the midazolam infusion was decreased by 0.05 mg/kg/h every 12–24 h.

Several of the sedative and analgesic agents including opioids (synthetic agents, morphine, and hydromorphone) as well as midazolam can be administered via the subcutaneous route. More recently, there is anecdotal experience with the subcutaneous administration of dexmedetomidine [76]. Concentrated solutions of fentanyl (25–50 μg/mL), midazolam (2.5–5 mg/mL), or dexmedetomidine (10–20 μg/mL) are used so that the maximum subcutaneous infusion rate does not exceed 3 mL/h. The subcutaneous infusions are started at the same dose that is currently being used for intravenous administration. A topical dermal anesthetic cream can be placed over the site of anticipated subcutaneous cannulation. Several areas are suitable for subcutaneous administration, including the subclavicular region, abdomen, deltoid, or anterior aspect of the thigh. The site is cleaned is prepped with a sterile antiseptic solution and then either a standard 22-gauge intravenous cannula or a 23-gauge butterfly needle is inserted into the subcutaneous tissue. Before placement, the tubing and needle are flushed with the opioid/benzodiazepine solution. The insertion site is then covered with a transparent, bio-occlusive dressing. The site should be changed every 7 days or sooner if erythema develops. The same infusion pumps that are used for intravenous administration can be used for subcutaneous administration. The pressure limit may need to be adjusted to allow for subcutaneous administration. Alternatively, a syringe pump can be used. If symptoms of withdrawal develop, additional boluses can be administered subcutaneously if necessary.

When a more prolonged course of opioid or sedative agent therapy will be necessary, switching to the oral administration of long-acting agents such as methadone or lorazepam

should be considered. This practice may allow for earlier removal of venous access and hospital discharge. To date, the majority of experience from the literature resides in the transition from intravenous opioids generally fentanyl to the oral agent, methadone. The reported advantages of methadone include its longer half-life allowing for dosing two to three times per day, an oral bioavailability of 75–90 %, and availability as a liquid. Although the first report regarding the use of methadone suggested a starting dose of 0.1 mg/kg every 12 h, the three patients in the series were receiving relatively low opioid doses and, therefore, higher doses of methadone were not needed [10]. Our subsequent clinical experience revealed that higher doses of methadone are needed especially following more protracted PICU courses and higher doses of fentanyl [77]. In that report, a 1:1 switch from fentanyl to methadone was used whereby the total daily dose of fentanyl was calculated and an equivalent dose of fentanyl was administered. So that a 10 kg patient receiving fentanyl at 10 μg/kg/h would be receiving a total daily fentanyl dose of 2,400 μg or 2.4 mg. Methadone would be started at 1.2 mg every 12 h by mouth. The fentanyl infusion is decreased by 50 % after the second dose of methadone, by 50 % after the third dose, and then discontinued after the fourth dose. The methadone was then weaned by 10 % every week as an outpatient. Although effective, the protocol did require a protracted weaning period and as such other investigators have suggested not only alternative ratios for the transition to oral methadone, but also more rapid weaning schedules [71, 72, 78–82]. When these studies are reviewed, there is up to a tenfold variation in the recommendations for the methadone dose when switching from intravenous opioids as well as variations in the initial dosing interval for methadone (every 6 versus 12 h). Some protocols have used intravenous methadone prior to oral methadone during the initial conversion process. Additionally, there is also significant variation in the rapidity with which the methadone is weaned, with some being as fast as 5 days. Regardless of the protocol used, close observation during the conversion period is necessary to avoid adverse effects from over-sedation or to recognize the early symptoms of withdrawal. Most importantly, those embarking on this practice are encouraged to review the available literature and develop their own hospital-based protocols. The efficacy and adverse effects of these protocols can then be monitored and adjusted as needed.

There remain some stigmata concerning the use of methadone. Therefore, a thorough discussion with the parents is necessary to discuss the need for methadone, its purpose, and the differences between addiction and physical dependency. Because of these issues as well as familiarity with long-acting morphine preparations, which are used in the treatment of children with chronic cancer-related pain, some physicians prefer to use the latter agent [83]. However, these agents are available only in tablets that cannot be crushed so that administration and subsequent weaning protocols may be more difficult in younger patients. Methadone on the other hand is available in a liquid formulation.

Additional issues with methadone include its pharmacokinetic profile as well as recent concerns from the adult literature regarding its potential effects on the QT interval and its association with increased mortality risks. Methadone undergoes metabolism by the P450 isoenzyme system of the liver making alterations in metabolism possible based on genetic factors and the co-administration of other medications [84]. The latter may be particularly problematic in the critically ill PICU patient. More recently concern has been expressed in the adult population, who are on maintenance methadone for drug addiction regarding the potential for death, of the potential for QT prolongation and arrhythmias [85–87]. To date, these reports are restricted to the adult population with no pediatric reports. However, these concerns have led to the consideration of obtaining periodic ECG's prior to and after instituting therapy with methadone especially in the adult population. Krantz et al. reviewed their recommendations from an expert panel convened to opine on these issues (Table 4.10) [86].

Although the majority of experience with transition to oral medications includes opioid therapy, there are also limited data to provide a groundwork for the transition from intravenous midazolam the oral lorazepam [77, 88]. As with opioids, the appropriate dose transition should consider the differences in the potency and half-life of the two medications as well as cross-over tolerance. Lugo et al. in a study evaluating enteral lorazepam to decrease midazolam requirements during mechanical ventilation suggested starting at a lorazepam dose that was 1/6th that of the total daily dose of intravenous midazolam [88].

Table 4.10 Recommendations for methadone therapy in adults

1. Inform patients of arrhythmia risk when prescribing methadone
2. History should include direct questioning for history of arrhythmia, structural heart disease, and syncope
3. Obtain a pretreatment ECG on all patients to measure the QTc
4. Obtain a follow-up ECG within 30 days of starting therapy and annually thereafter
5. More frequent ECG's should be obtained for the following:
(a) Methadone dose greater than 100 mg/day
(b) Unexplained syncope or seizures
6. If the QTc is ≥450 ms, but less than 500 ms; discuss risk-benefit ratio with patient and monitor more frequently
7. If the QTc is ≥500 ms, consider:
(a) Discontinuing methadone or reducing dose and using alternative medications
(b) Eliminate contributing factors such as drugs that promote hypokalemia
8. QT prolongation may be exacerbated by:
(a) Other medications
(b) Co-morbid medical conditions
(c) Medications that alter methadone metabolism

Based on data from Krantz et al. [86]

In addition to opioids, non-opioid agents including the benzodiazepine, diazepam, has been used to treat opioid withdrawal in neonates and infants [89]. The majority of these data come from trials evaluating therapies in neonates born to drug-addicted mothers. When benzodiazepines have been used, clinical studies have demonstrated adverse effects on behavior in the neonatal population including increased sedation and poor sucking as well as poor control of the autonomic hyperactivity that occurs with opioid withdrawal [90]. Similar results have been demonstrated with the use of phenobarbital [91, 92]. Phenothiazines (chlorpromazine) have also been used in the treatment of infants of drug-addicted mothers [93]. Despite relative success with an efficacy equivalent to that of phenobarbital, adverse effects including α-adrenergic blockade with hypotension and a lowering of the seizure threshold have limited their widespread application [94].

The centrally acting, α_2-adrenergic agonist, clonidine, has been used to treat and prevent opioid withdrawal in both neonates and adults [95–97]. The α_2-adrenergic receptors mediate part of their pharmacologic actions through the activation of the same potassium channel as opioid receptors. Because of its prolonged duration of action (12–18 h), in most cases, twice a day dosing may be possible with starting doses range from 3 to 5 μg/kg/day. Adverse effects from clonidine include sedation, bradycardia, and hypotension. Although the use of clonidine is becoming more widespread in pediatric anesthesia as a premedicant for the operating room as well as for caudal/epidural anesthesia; to date, there is limited clinical experience with its use in the treatment of opioid withdrawal. A nicely performed, prospective trial recently evaluated the efficacy of clonidine as an adjunct to the treatment of withdrawal in infants with intrauterine exposure to methadone or heroin and neonatal abstinence syndrome, defined as two consecutive modified Finnegan scores ≥9 [98]. The cohort for the study included 80 infants, all of whom received standard therapy with oral tincture of opium according to a standardized algorithm and were randomly assigned to receive oral clonidine (1 μg/kg every 4 h) or placebo. The median length of therapy was 27 % shorter in the clonidine group when compared to the placebo group. However, in the clonidine group, seven infants required restarting opium after its initial discontinuation versus none in the placebo group. Higher doses of opium were required in the placebo group and there was a higher incidence of treatment failures (12.5 % versus 0 %). Hypertension, hypotension, bradycardia, or desaturations did not occur in either group. Three infants in the clonidine group died as a result of myocarditis, sudden infant death syndrome, and homicide, all after hospital discharge and before 6 months of age. Further information is needed to more clearly define the efficacy and safety of clonidine as well as its role in treating opioid withdrawal in the PICU patient. An additional advantage of clonidine is the availability of a transdermal patch which may be used instead of oral administration although dose titration and weaning may be problematic given the limited number of sizes of the transdermal system.

Dexmedetomidine (Precedex®, Hospira Worldwide Inc, Lake Forest, IL) is the pharmacologically active dextroisomer of medetomidine. Like clonidine, it exerts its physiological effects via α_2-adrenergic receptors. Regardless of the agent or agents responsible for withdrawal, the role of dexmedetomidine in treating such problems is supported by animal studies [99–102], case reports in adults and children [103–107], and one retrospective case series in infants [108]. The latter is a retrospective review that outlines the use of dexmedetomidine to control withdrawal is a retrospective review of seven infants ranging in age from 3 to 24 months [108]. The patients had received a continuous fentanyl infusion supplemented with intermittent doses of midazolam for sedation during mechanical ventilation. Withdrawal was documented by a Finnegan score ≥12. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/h followed by an infusion of 0.5 μg/kg/h. The loading dose was repeated and the infusion increased to 0.7 μg/kg/h in the two patients who had received the highest doses of fentanyl (8.5 ± 0.7 versus 4.6 ± 0.5 μg/kg/h, $p < 0.0005$). Withdrawal was controlled and subsequent Finnegan scores were ≤7.

Conclusion

When sedative and analgesic agents are administered, adverse effects on physiologic function may follow [3, 40]. Monitoring of the patient's physiologic function is mandatory whenever these agents are in use. There is also an increased understanding and recognition of withdrawal syndromes which may occur following the prolonged administration of sedative and analgesic agents. Strategies are needed to identify those patients at risk for withdrawal followed by appropriate interventions to prevent or treat it. These may include a gradual tapering of the infusion rate or switching to oral or subcutaneous administration. As this is an increasing problem in the PICU setting, newer strategies to prevent its occurrence such as the use of NMDA antagonists or rotating sedation regimens warrant further investigations. With these caveats in mind, the goal of providing effective and safe sedation and analgesia for all of our patients is within reach.

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Neuromuscular Blockade

5

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Abstract

Since the introduction of the neuromuscular blocking agents (NMBAs) in anesthesia in 1942, a marked evolution has occurred in these drugs. Currently, there are many recognized indications to starting treatment with a NMBA in critically ill children. These may be categorized as short-term, to facilitate procedures, or long-term (sustained neuromuscular blockade), as therapeutic interventions. Atracurium or vecuronium administered by continuous infusion are the choice for the majority of PICU children requiring neuromuscular blockade, however, intermittent doses of pancuronium may be considered as well. Neuromuscular blockade complications can be classified as short-term (accidental extubation, disconnection of the mechanical ventilator), medium-term (edema, venous thrombosis) and long-term (prolonged paralysis, muscle atrophy). Monitoring the neuromuscular blockade level (clinical examination and peripheral nerve stimulation) is recommended and allows the use of lower doses of NMBAs, which may minimize these side effects. Train-of-four is the more commonly used method and involves electrical stimulation of a peripheral motor nerve with four sequential stimuli over a two second period and observation of the responses of a muscle innervated by the stimulated nerve. Adequate neuromuscular blockade reversal is essential for restoring and maintaining laryngeal reflexes, respiratory effort and motor function. Recovery may be obtained by using agents that reverse the action of NMBAs, such as anticholinesterase drugs (neostigmine, edrophonium and pyridostigmine) or cyclodextrins (sugammadex).

Keywords

Neuromuscular blocking agents • Neuromuscular blockade • Neuromuscular junction • Neuromuscular block

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Introduction

Since the introduction of the neuromuscular blocking agents (NMBAs) in 1942, a marked evolution has occurred in these drugs. In association with the introduction of vecuronium and atracurium, the most widely used NMBAs in critically ill patients, there was a significant increase in the indications for neuromuscular blockade. This expansion was partially provided by the new ventilatory modes and technologic advances that necessitated cooperative, sedate, or immobile patients. In addition, there was an expansion of knowledge regarding available NMBAs which, in turn, led to greater

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use of muscle paralysis in the intensive care unit (ICU). It should be noted that the NMBAs do not have sedative, amnestic, or analgesic properties, thus, the concurrent administration of sedative and analgesic drugs is mandatory to provide these effects.

Physiology of Neuromuscular Blocking

The neuromuscular junction consists of a motor nerve terminal, the synaptic cleft, and the postsynaptic muscle endplate (Fig. 5.1). The nicotinic receptor of the skeletal muscle is a pentamer composed of four subunits (α, β, γ, and δ). In mature, muscle endplates, the γ subunit is replaced by ε subunit (Fig. 5.2). The five subunits are arranged around a pseudo-axis of symmetry to circumscribe a channel [1–3]. Agonist-binding sites are found at the subunit interfaces; in muscle, only two of the five subunits interfaces, αγ and αδ, have evolved to bind ligands. Both of the subunits forming the subunit interface contribute to ligand specificity. The binding of agonists and reversible competitive antagonists involves overlapping surfaces on the receptor. The agonist-binding site is intimately coupled with an ion channel in the muscle receptor, such that simultaneous binding of two agonist molecules results in a rapid conformational change that opens the channel.

The nerve synthesizes acetylcholine and stores it in vesicles (Fig. 5.3). The approach of an action potential at the distal motor nerve ending leads to an instant opening of voltage gated calcium channels with a subsequent abrupt increase in intracellular calcium concentration [4]. The motor endplate contains specialized nicotinic acetylcholine receptors, which convert the chemical signal into an electrical signal. Nicotinic acetylcholine receptors, after activation by the acetylcholine, respond by opening their channels for influx of sodium ions into the muscle to depolarize the muscle. The endplate potential created is transmitted along the muscle membrane by opening of the sodium channels, leading to muscle contraction [4]. Acetylcholine immediately detaches from the

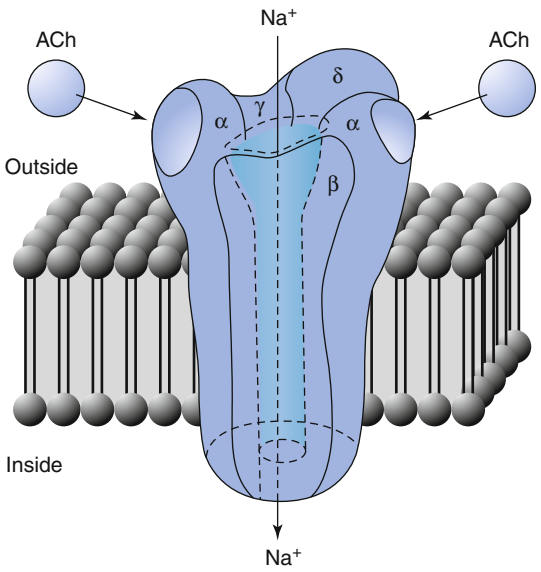


Fig. 5.2 The acetylcholine receptor

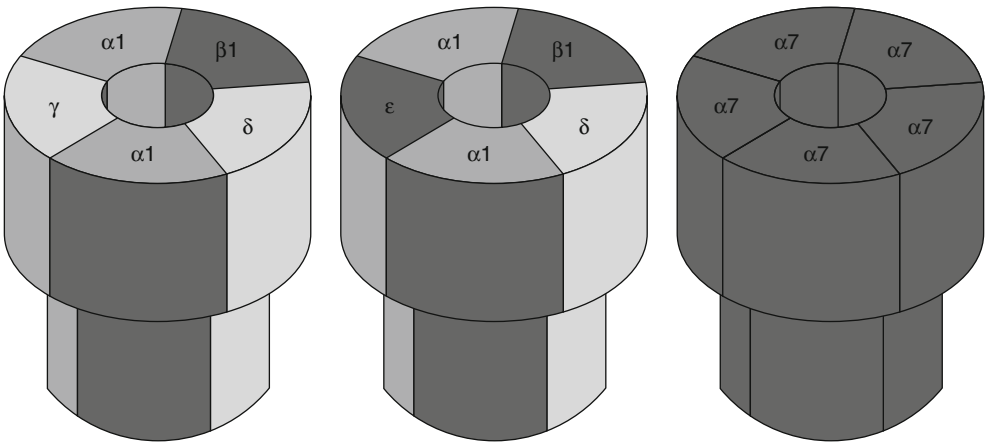


Fig. 5.1 Sketch of postsynaptic nicotinic acetylcholine receptor channels. The mature, or junctional, receptor consists of two α1-subunits and one each of β1-, δ-, and ε-subunits. The immature, extra-junctional or fetal form consists of two α1- and one each of β1, δ, and γ-subunits. The latter is thus called c-subunit receptor. Recently, a neuronal receptor consisting of five subunits of α7 has been described in muscle. All subunits are arranged around the central cation channel. The immature isoform containing the γ-subunit shows long open times and low-amplitude channel currents (not shown). The mature isoform containing the ε-subunit shows shorter open times and high-amplitude channel currents during depolarization. Substitution of the ε-subunit for the γ-subunit gives rise to the fast-gated, channel with prolonged open time. As expected, acetylcholine application to the α7 ηAChR also results in a fast, rapidly decaying inward current (not shown). All of these depolarizing events are insensitive to the treatment with atropine but sensitive to treatment with α-bungarotoxin or non-depolarizing NMBAs, blocking current flow (Reprinted from Martyn et al. [3]. With permission from John Wiley & Sons, Inc.)

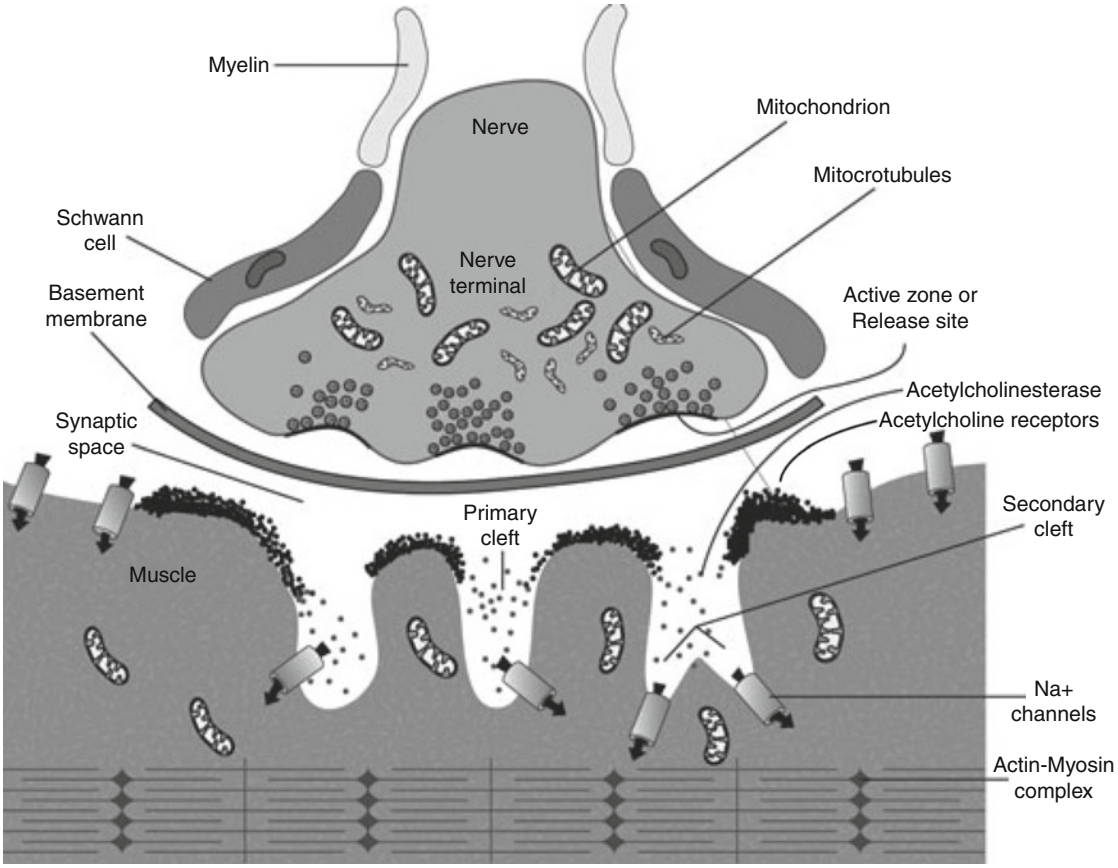


Fig. 5.3 Structure of the adult neuromuscular junction with the three cells that constitute the synapse: the motor neuron (i.e. nerve terminal), muscle fibre and Schwann cell. As the nerve approaches its muscle fibres, and before attaching itself to the surface of the muscle fibre, the nerve divides into branches that innervate many individual muscle fibres. The motor nerve loses its myelin and further subdivides into many presynaptic boutons to terminate on the surface of the muscle fibre. The nerve terminal, covered by a Schwann cell, has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side and mitochondria and microtubules toward its other side. A synaptic gutter or cleft, made up of a primary and many secondary clefts, separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. The sodium channels are present at the bottom of the clefts and throughout muscle membrane. The acetylcholinesterase, proteins and proteoglycams which stabilise the neuromuscular junction are present in the synaptic clefts (Reprinted from Martyn et al. [3]. With permission from John Wiley & Sons, Inc.)

receptor and either diffuses back into the nerve terminal or is pulled down by the acetylcholinesterase in the synaptic cleft. Depolarization ends when acetylcholine unbinds from the receptor.

Neuromuscular blocking agents are structurally related to acetylcholine and act by interfering with the binding of acetylcholine to the motor endplate. They are divided into depolarizing and nondepolarizing agents, based upon their mechanism of action. Depolarizing neuromuscular blocking agents simulate the effect of acetylcholine and thus can be considered agonists despite the fact they block neurotransmission after initial stimulation. Their initial action is to depolarize the membrane by opening channels in the same manner as acetylcholine. However, they persist for longer durations at the neuromuscular junction mainly because of their resistance to acetylcholinesterase. The depolarization is therefore longer-lasting and is followed by neuromuscular transmission blockade and flaccid paralysis. The block is due to perijunctional sodium channels closing that will not reopen until the endplate is repolarized. These closed perijunctional channels keep the depolarization signal from affecting downstream channels.

The depolarizing neuromuscular blocking agents are not susceptible to hydrolysis by acetylcholinesterase and thus are not eliminated from the synaptic cleft until after they are eliminated from the plasma. Because calcium does not diffuses back in the sarcoplasmic reticulum, muscles are refractory to repeat depolarization, until depolarizing neuromuscular blocking agents pass from the receptor to the circulation and are hydrolyzed by plasma pseudocholinesterase.

Nondepolarizing neuromuscular blocking agents also bind acetylcholine receptors but do not activate them. Nondepolarizing neuromuscular blocking agents impair neurotransmission by competitively preventing the binding

of acetylcholine to its receptor. Drug binding to the acetylcholine receptor either prevents the conformational change in the receptor or physically obstructs the ion channels so that an endplate potential is not generated.

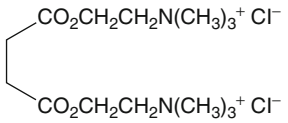


Fig. 5.4 Chemical structure of succinylcholine (Courtesy of William Joe Wheeler, PhD)

Types and Classes of Neuromuscular Blocking Agents

The number of NMBAs has increased since curare was first used medically in 1912 and in anesthesia in 1942 [5]. Both succinylcholine and pancuronium, introduced in 1952 [6] and 1967 [7], respectively, are still used today. Vecuronium [8] and atracurium [9] were subsequently added in the 1980s. Mivacurium [10] and rocuronium [10] were introduced in the 1990s. Other agents included gallamine (1951) [11], alcuronium (1964) [12], fazadinium (1976) [13], pipecuronium (1980) [14], doxacurium (1988) [15], cisatracurium (1996) [16], and rapacuronium (1999) [17]. Recently, neuromuscular drug development has included the investigational drugs gantacurium [18] and AV002, which self-destruct by endogenous chemical processes. The "ideal NMBA" for use in intensive care produces an early, titratable paralysis, has a moderately rapid offset of action (less than 15 min) to allow for repeated neurologic assessment, no adverse hemodynamic or other adverse physiologic effects, elimination independent of hepatic or renal function, inactive metabolites, no propensity to accumulate, stability over 24 h to allow for continuous infusion, and modest cost [19].

Depolarizing Neuromuscular Blocking Agents

Succinylcholine

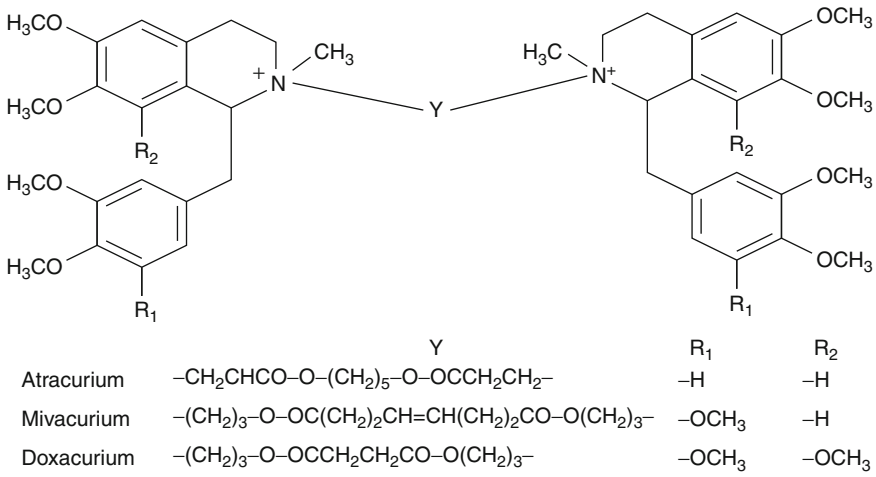
Succinylcholine (also known as suxamethonium chloride) is the only depolarizing neuromuscular blocking agent in clinical use within the United States. Structurally, it resembles two molecules of acetylcholine joined back to back by an ester linkage (Fig. 5.4). A unique combination of rapid onset and ultra-short duration of action make succinylcholine especially useful for facilitating tracheal intubation. In the critical care setting, the use of succinylchloride is restricted to emergency tracheal intubation because of the many complications associated with its use. Once the airway has been successfully controlled, if there is an ongoing need for neuromuscular blockade, a nondepolarizing agent is administered. Elimination depends on hydrolysis by butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase).

Dose-response studies suggest that infants require at least 3 mg/kg and children 2 mg/kg of succinylcholine to produce reliable conditions for tracheal intubation [20]. The duration of action of these doses is the about the same or somewhat less than that of the standard 1 mg/kg intubating dose in adults (6–8 min). In the absence of intravenous access intramuscular administration doses of 5 mg/kg for infants and 4 mg/kg for children have been shown to produce 85–100 % twitch depression [21]. When given by this route, one can expect maximum onset of blockade within 3–5 min and duration of action of between 19 and 23 min. The increased dose requirement of succinylcholine in younger patients is thought to result from its rapid distribution into an enlarged volume of extracellular fluid rather than an altered response to the action of the drug at postjunctional acetylcholine receptors [20]. Approximately 1 in 3,200 patients is homozygous for a defective pseudocholinesterase and may remain paralyzed for 3–8 h after a single dose [22]. Although neonates and infants aged less than 6 months have only half the concentration of butyrylcholinesterase activity of adults, this does not prolong the effect of succinylcholine.

Significant adverse effects include hypertension, tachycardia, bradycardia, ventricular arrhythmias, hyperkalemia, and, less commonly, increased intracranial pressure or malignant hyperthermia (Table 5.1) [23]. The increase in serum potassium is mediated by the simultaneous opening of large numbers of nicotinic acetylcholine receptors and is approximately 0.5 mEq/dL [24]. Succinylcholine is contraindicated after the acute phase of major thermal injury. Following thermal injury, extrajunctional acetylcholine receptor expression increases in proportion to the magnitude of the burn [25]. This results in an exaggerated release of potassium after administration of succinylcholine – indeed, profound hyperkalemia associated with cardiac arrest in this situation may occur. Succinylcholine should not be administered to patients beyond 48 h from the time of injury and remains contraindicated for 6–12 months. Succinylcholine is also one of the classic triggers for malignant hyperthermia and should not be administered to patients with a history, or family history, of this disorder. Other side effects include cardiac dysrhythmias, masseter spasm, and increased intraocular, intracranial, and intragastric pressure. Diffuse muscle pain may occur following succinylcholine administration. For these reasons, a so-called "defasiculating dose" of a nondepolarizing neuromuscular blocking drug (typically one-tenth of the normal dose) is often administered shortly before administering succinylcholine, though the evidence for this practice is limited.

Table 5.1 Succinylcholine, its side effects and relative contraindications

Side effect	Mechanism
Muscle soreness/pain	Fasciculations due to initial depolarization of the NMJ (may be prevented with the use of a defasciculating dose, typically one-tenth dose of a NDNMB, e.g. 0.01 mg/kg vecuronium)
Hyperkalemia	SCh will typically raise serum K^+ 0.5–1 mEq/L due to initial depolarization of the NMJ (serious and life-threatening hyperkalemia may occur with renal failure or when extrajunctional AChR are upregulated (crush injury, burns, disuse atrophy, muscular dystrophy) ***Contraindications***: 1. ***Pre-existing hyperkalemia*** 2. ***Acute renal failure or chronic renal insufficiency*** 3. ***History of trauma, burns, crush injury (at risk period occurs between 48 h and 120 days of post-injury)*** 4. ***Disuse atrophy, neuromuscular diseases (e.g. Duchenne's muscular dystrophy)***
Malignant hyperthermia (syndrome characterized by unremitting muscle rigidity, hyperthermia, hypercapnia, and metabolic acidosis)	Mechanism not completely understood ***Contraindicated in patients with family history of malignant hypertension***
Increased intraocular pressure	Contraction of extraocular muscles during initial depolarization of NMJ (may be prevented with "defasciculating dose") ***Contraindications:*** 1. ***Glaucoma*** 2. ***Open globe injury***
Increased intracranial pressure	Fasciculations and muscle rigidity (may be prevented with "defasciculating dose") ***Use with caution in patients with head injury***
Increased intragastric pressure	Contraction of abdominal muscles (may be prevented with "defasciculating dose") ***Use with caution in patients with full stomach (increased risk of aspiration)***
Prolonged neuromuscular blockade	Plasma pseudocholinesterase deficiency (liver disease, pregnancy, h/o oral contraceptive use, familial pseudocholinesterase deficiency)



	Y	R_1	R_2
Atracurium	$-CH_2CHCO-O-(CH_2)_5-O-OCCH_2CH_2-$	–H	–H
Mivacurium	$-(CH_2)_3-O-OC(CH_2)_2CH=CH(CH_2)_2CO-O(CH_2)_3-$	$-OCH_3$	–H
Doxacurium	$-(CH_2)_3-O-OCCH_2CH_2CO-O(CH_2)_3-$	$-OCH_3$	$-OCH_3$

Fig. 5.5 The benzylquinolinium family of non-depolarizing NMBAs (Courtesy of William Joe Wheeler, PhD)

Non-depolarizing Neuromuscular Blocking Agents

The clinically available non-depolarizing neuromuscular blocking agents can be classified into benzylquinolinium (Fig. 5.5) or aminosteroid (Fig. 5.6) compounds. Agents in both groups are quaternary ammonium compounds that contain a positively charged nitrogen atom capable of binding to the alpha subunit(s) of the nicotinic acetylcholine receptor. Benzylquinolium drugs are associated with histamine release and hypotension, whereas aminosteroid compounds are associated with tachycardia and hypertension. Table 5.2 provides dosing administration on the commonly used non-depolarizing neuromuscular blocking agents in the PICU.

Aminosteroid Compounds

Pancuronium

Pancuronium is a potent, long-acting, bisquaternary aminosteroidal neuromuscular blocking agent (Fig. 5.7). It is a synthetic aminosteroid that has an onset of action of 2–3 min

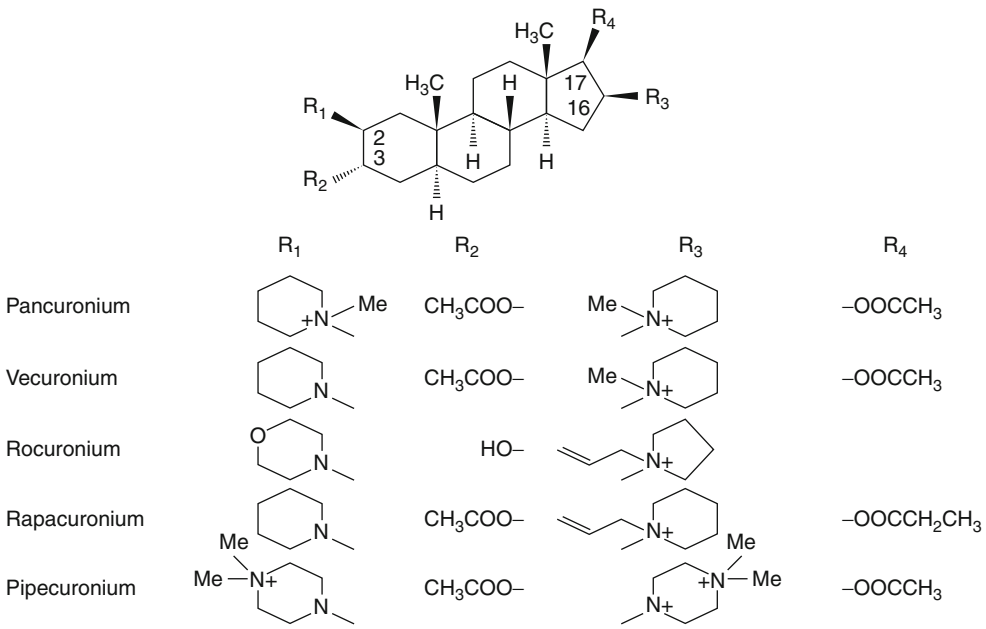


Fig. 5.6 The aminosteroid family of non-depolarizing NMBAs (Courtesy of William Joe Wheeler, PhD)

Table 5.2 Recommended neuromuscular blocking agents

Agent	Bolus or intermittent injection (μg/kg/dose)	Infusion rate	Onset (min)	Duration (min)	Duration of action	Note
Pancuronium	50–100 Given as required 4–6 h	–	2–4	90–100	Long	Renal and hepatic elimination Reduce dosage in neonates Vagolysis causes tachycardia
Vecuronium	80–100	50–100 μg/kg/h	1–3	35–45	Intermediate	Hepatic and renal elimination Reduce dosage in neonates Little histamine release Few cardiovascular effects
Rocuronium	600	300–600 μg/kg/h	0.8–1.5	30–60	Intermediate	Hepatic elimination Rapid onset Few cardiovascular effects
Atracurium	300–600	0.3–1.7 mg/kg/h	1–3	25–30	Intermediate	Hofmann elimination; hydrolysis by plasma esterases May cause cardiovascular effects due to histamine release Relatively safe in renal or hepatic failure
Cisatracurium	150	60–180 μg/kg/h	2–3	40–45	Intermediate	Hofmann and renal elimination. Little histamine release Few cardiovascular effects Higher doses may be required
Mivacurium	200	1–15 μg/kg/min	1–2	<30	Intermediate	Renal elimination. Histamine release in rapid infusions Prolonged neuromuscular blockade in cases of plasma cholinesterase deficiency or renal failure

Based on data Playfor et al. [40]

and half-life of 110 min. Excretion is accomplished primarily by renal routes, although hepatic elimination plays a role. As such, it is contraindicated in patients with significant kidney or liver dysfunction. Pancuronium has an active metabolite, 3-hydroxypancuronium, with 30–50 % of the potency of the parent compound. Adverse cardiovascular effects associated

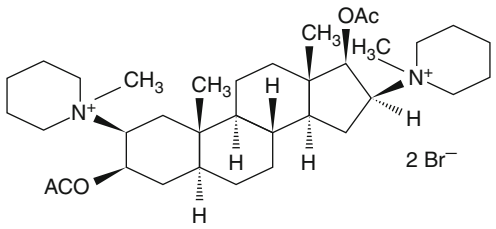


Fig. 5.7 Chemical structure of pancuronium (Courtesy of William Joe Wheeler, PhD)

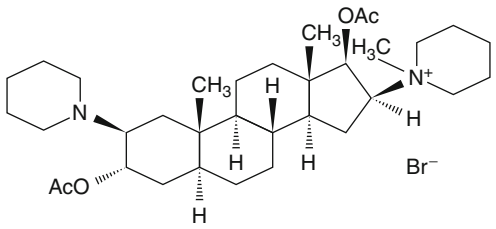


Fig. 5.8 Chemical structure of vecuronium (Courtesy of William Joe Wheeler, PhD)

with pancuronium include tachycardia, hypertension, and increased cardiac output due to vagal blockade and noepinephrine release. More than 90 % of ICU patients will have an increase in heart rate of ≥10 beats/min, which limits its use in patients who cannot tolerate an increase in heart rate. An open label study carried out to evaluate the efficacy and dose requirements in critically ill children have shown that the majority of patients required 0.05–0.08 mg/kg/h and that there was a tenfold variability in infusion requirements [26]. Several factors might have accounted for the variability in infusion requirements including interactions with other medications and tachyphylaxis following prolonged infusion [26].

Vecuronium

Vecuronium is amonotertiary, monoquaternary aminosteroid relaxant produced by N-demethylation in the 2-piperidino substitution of pancuronium (Fig. 5.8). This structural alteration considerably reduces the vagolytic effects (tachycardia and hypertension) observed with pancuronium. It has an onset of action of 1–3 min and duration of 30–40 min (dose dependent). It has a safe cardiovascular profile and does not affect heart rate or blood pressure. Like pancuronium, it has an active metabolite, 3-desacetylvecuronium, with 80 % of the potency of the parent compound. Differences in volume of distribution produce a longer duration of action in younger children. A study conducted to determine the appropriate vecuronium infusion rates demonstrated that neonates and infants required less 45 % less vecuronium (mean infusion rate 54.7 μg/kg/min) than older children (mean 98.7 μg/kg/min) and had a faster spontaneous recovery to 70 % train of four at one response (T4/T1) than older children (45 *vs* 65 min, respectively), with no evidence of prolonged weakness in a PICU population [27]. A randomized controlled trial comparing cisatracurium and vecuronium infusions in a PICU has found that vecuronium rate infusion averaged mean 2.6 ± 1.3 μg/kg/min with a median duration of 40 h while the median time to recovery was significantly shorter with cisatracurium (52 min, 35–73) compared with vecuronium (123 min, 80–480). Prolonged recovery of neuromuscular function (>24 h) occurred in one child (6 %) on vecuronium group [28].

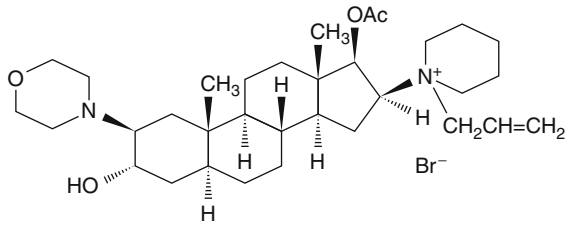


Fig. 5.9 Chemical structure of rocuronium (Courtesy of William Joe Wheeler, PhD)

Pipecuronium

Pipecuronium is an aminosteroid, bisquaternary, long-acting agent similar to pancuronium in structure, potency, and duration of effect, but without the vagolytic actions of pancuronium. It is eliminated mainly by the kidneys (70–80 %), and a small fraction is eliminated through the bile after being metabolized in the liver. There appears to be little difference, other than cost, in long-term administration of pancuronium versus pipecuronium in the critical care setting. Pipecuronium is no longer available in the United States or Canada, but it may be available elsewhere. There are no available studies in critically ill children assessing this agent.

Rocuronium

Rocuronium (rapid onset-curonium) is a desacetoxy analogue of vecuronium with a more rapid onset of action (Fig. 5.9). Although similar to vecuronium in pharmacokinetics, it has a more rapid onset of action and a lack of active metabolites. The onset of action in children is about 30–60 s and the duration is 30–40 min (equal in children and adults). It is metabolized by the liver (50–60 %) with 33 % excreted unaltered in the urine. Due to its time to onset makes it the most attractive alternative, optimal dose of 1 mg/kg, when succinylcoline is contraindicated for rapid sequence tracheal intubation [29]. A prospective study evaluating rocuronium by continuous infusion to provide neuromuscular blockade in the PICU showed that dose requirements ranged in the majority of patients from 0.3 to 1 mg/kg/h while the variability in dose reached a maximum of 2.2 mg/kg/h [30]. Although there was an increase in requirement noted each day, this did not reach statistical significance until day 5.

The highest infusion rate occurred in patients that were receiving rocuronium more than 5 days. The wide variability in requirements and changes in requirements over time support the routine monitoring of neuromuscular function [30].

Rapacuronium

Rapacuronium was marketed as an alternative to succinylcholine. It was withdrawn from the market on March 2001, because of reports of morbidity (bronchospasm) and mortality associated with its use.

Benzylquinolinium Compounds

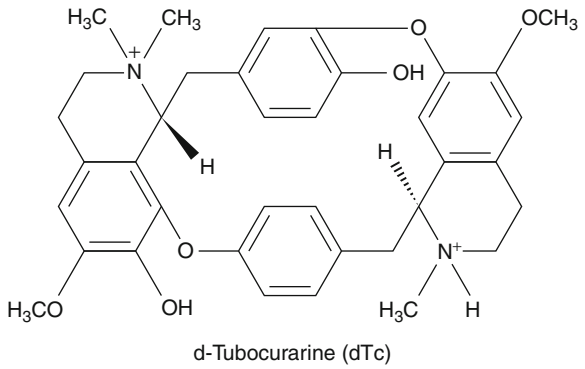
These agents are esters, and metabolism via ester hydrolysis occurs, to some extent, with each member of the group. Some (atracurium and cisatracurium) also undergo a nonorgan-based degradation known as Hofmann elimination. Histamine release, and its effect on cardiac and respiratory function, has been a relatively consistent concern over the years with this group of agents.

D-tubocurarine

This long-acting benzylisoquinolinium agent is rarely used in ICUs because it induces histamine release and autonomic ganglionic blockade. Tubocurarine (Fig. 5.10) is no longer available in the United States or Canada, but it may be available elsewhere. It causes dose- and rate-dependent histamine release and is associated with arterial hypotension following rapid infusions of large doses. Histamine-associated hypotension can be minimized by slow injection, incremental dose increases, and coadministration of histamine-1 and histamine-2 receptor blockers. Metabolism and elimination are affected by both renal and hepatic dysfunction.

Atracurium

Atracurium (Fig. 5.11), a mixture of ten stereoisomers, is a bisquartenary benzylisoquinoline diester with an intermediate duration of clinical action. The molecule is degraded by both pH- and temperature-dependent Hofmann elimination (autolysis) and by ester hydrolysis; it therefore does not require a dosage adjustment in patients with renal or hepatic failure. This agent is usually administered by continuous infusion in a critical care setting. When assessed in PICU patients, the mean duration of infusion was found to be 98 h (range 36–284 h) during which an increasing dose requirement was observed in all patients. The mean infusion rate of atracurium was 1.60 ± 0.08 mg/kg/h and 1.72 ± 0.15 mg/kg/h at 72 h [31]. Hence, prolonged infusions may be associated with the development of tolerance, necessitating significant dose increases or conversion to other NMBAs. Laudanosine



d-Tubocurarine (dTc)

Fig. 5.10 Chemical structure of d-Tubocurarine (Courtesy of William Joe Wheeler, PhD)

is a breakdown product of Hofmann elimination of atracurium and has been associated with central nervous system excitation. This has led to concern about the possibility of precipitating seizures in patients who have received extremely high doses of atracurium. Initial concerns about the use of this agent in the ICU may have been the result of fear regarding a possible association between atracurium administration and seizure activity in dogs. However, it is unlikely to be of clinical significance in humans [32].

The adverse effects associated with atracurium relate mainly to histamine release. This commonly results in a macular rash or erythema along the course of the vein of injection, which may subsequently spread peripherally. Occasionally, the rash may be accompanied by more serious histamine-mediated effects such as hypotension, tachycardia or bonchospasm.

Cisatracurium

Cisatracurium besylate (Fig. 5.12), an intermediate-acting benzylisoquinolinium NMBA, is one of ten stereoisomers of atracurium with several advantages over atracurium, including a threefold increased potency, slower onset of action, lack of dose-related histamine release in doses up to eight times the 95 % effective dose, and a higher ratio of autonomic-to-neuromuscular blockade dose. Mean recovery time in critically ill children is approximately 52 min (35–73 min) following cessation of infusion [28]. Cisatracurium dose ranges for children in the PICU have averaged from 1.4 to 22.7 μg/kg/min [28, 33, 34] while the mean total duration of infusion was approximately 65 h [28, 34]. A significant increase in dose may be required in 30–70 % of children receiving cisatracurium, suggesting tachyphylaxis phenomena [28, 33]. Cisatracurium demonstrated a fast recovery of neuromuscular function after its discontinuation [28, 34]. The safety of cisatracurium and its lack of active metabolites make it a reasonable choice for use in critically ill patients.

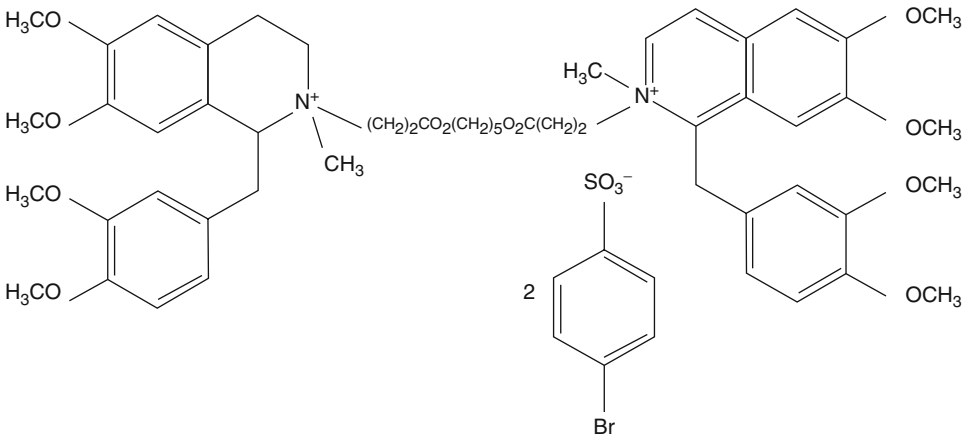


Fig. 5.11 Chemical structure of atracurium (Courtesy of William Joe Wheeler, PhD)

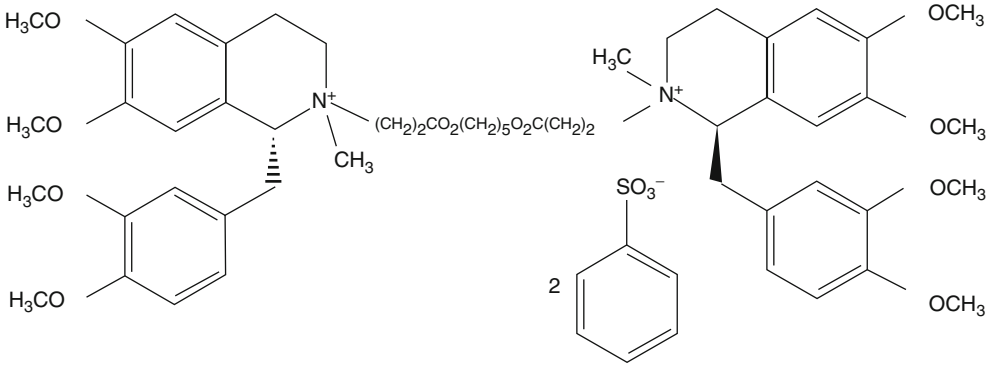


Fig. 5.12 Chemical structure of cis-atracurium (Courtesy of William Joe Wheeler, PhD)

Doxacurium

Doxacurium, a long-acting benzylisoquinolinium agent, is the most potent NMBA currently available. It is similar to pancuronium in its elimination half-life and dependence on renal clearance, but does not cause tachycardia or have other hemodynamic effects. Initial doses of doxacurium 0.05–0.1 mg/kg may be given with maintenance infusions of 0.3–0.5 μg/kg/min and adjusted to the degree of blockade desired. An initial bolus dose lasts an average of 60–80 min. Doxacurium is primarily eliminated by renal excretion. Doxacurium has a slow onset of action and a long duration of effect. It is used infrequently in a adult critical care setting, and there is limited information regarding administration by infusion. There are no studies in pediatric population.

Mivacurium

Mivacurium has a structure similar to that of atracurium but a shorter duration of action, a half-life of approximately 2 min. Mivacurium is hydrolysed by plasma cholinesterase at 88 % of the rate of succinycholine, this produces duration of action approximately twice that of succinycholine. Plasma clearance of mivacurium decreases with age consistent with the faster recovery times and greater infusion requirements reported in infants and children compared with adults. There are no available data to support its use as a continuous infusion in the PICU.

Indications for Neuromuscular Blockade

There are many recognized indications to starting treatment with a NMBA in critically ill children. These may be categorized as short-term, to facilitate procedures, or long-term (sustained neuromuscular blockade), as therapeutic interventions.

Short-Term Indications

The most important indication for the use of muscle relaxants during respiratory failure and in patients who need urgent or rapid control of airway is to facilitate tracheal intubation. Because of the short circulation times of neonates and infants, muscle relaxants are very rapidly distributed to the effect sites and have short onset times. The second set of indications of muscle relaxants include maintenance of

flaccid muscles or immobilized patient for some imaging studies, to ensure patient safety and successful completion of a diagnostic or therapeutic procedure.

Long-Term Indications: Sustained Neuromuscular Blockade

There are some studies assessing practice of analgesia, sedation, and neuromuscular blockade within PICU in the USA [35] and the UK [36]. These studies found that NMBA were used in 30 % of ventilated patients. In fact, this apparently high percentage has gone unchanged over the past 15 years being higher than rate of 13 % reported in studies of critically ill adults.

There are many recognized indications for the sustained use of neuromuscular blockade in PICU patients. The most common indication include the facilitation of mechanical ventilation to prevent respiratory dysynchrony, stop spontaneous respiratory efforts and muscle movement, improve gas exchange and facilitate less physiological techniques such as permissive hypercapnia, inverse ratio ventilation or high frequency oscillatory ventilation.

The results from a recent study (ARDS et Curarisation Systematique – ACURASYS) suggest a potential role for NMB in the management of patients with acute respiratory distress syndrome (ARDS) has been specifically studied in adults [37]. The ACURASYS study proposes use of NMBAs in early ARDS, but their use should be applied in the appropriate patient population and clinical setting. Hence, this study suggests that early use of cistratracurium (i.e., within 8 h of ARDS diagnosis) may be appropriate in critically ill adults with severe ARDS (i.e., $PaO_2/FiO_2 < 120$ mmHg) when sedation and analgesia alone is inadequate in providing conditions for effective mechanical ventilation. Further studies will be required to assess whether duration of neuromuscular blockade affects mortality and whether this benefit can be applied to other neuromuscular blocking agents, and to ascertain the mechanism behind the benefit of paralysis.

Additional indications include management of increased intracranial pressure, pulmonary hypertension, treatment of muscle contractures associated with tetanus, neuroleptic malignant syndrome, malignant hyperthermia, management of hypothermia in order to block the thermoregulatory response. In some surgical patients, MNBAs allow protecting surgical repairs in the immediate postoperative period such as cricoid split procedures, tracheal reconstruction and vascular anastomoses.

Current Treatment Strategies

In 1995, the Society of Critical Care Medicine published a review establishing the best practice parameters for the use of NMBAs. The recommendations concerning the use of NMBAs included (a) the use of pancuronium as the preferred NMBA for most critically ill patients and (b) the use of vecuronium as the first option in patients with cardiac disease or hemodynamic instability, with lower doses in patients with renal or hepatic failure [38]. However, this consensus was made for adult population. NMBAs may be administered by intermittent injection or continuous intravenous infusion. For critically ill children, continuous infusions may be chosen to maintain a stable, baseline level of blockade and thereby avoid periods of decreased blockade. There are some authors that recommend the intermittent bolus administration because it allows [39] monitoring and titration of drug in addition to periods of normal neuromuscular function [40]. However, there is no clear evidence that one method of administration is superior to another.

The United Kingdom Paediatric Intensive Care Society's Sedation, Analgesia and Neuromuscular Blockade Group published a set of consensus guidelines to help clinicians manage critically ill children requiring sustained neuromuscular blockade [40]. The consensus assigned grades of recommendation according to strength and quality of the scientific evidence:

1. Analgesia and sedation should be appropriately provided before administering neuromuscular blocking agents (Grade of recommendation = D).
2. Children receiving neuromuscular blockade should be regularly assessed and discontinued from NMB agent as soon as possible (Grade of recommendation = D).
3. When judged to do so, continuous infusions of neuromuscular blocking agents should be discontinued at least once every 24 h until spontaneous movement returns and the levels of analgesia and sedation can be assessed (Grade of recommendation = C).
4. Atracurium or vecuronium administered by continuous infusion are the choice for the majority of PICU children requiring neuromuscular blockade. Intermittent doses of pancuronium may be considered (Grade of recommendation = D).
5. Children receiving continuous infusions of NMB agent should be assessed at least once every 24 h with train-of-four monitoring. Administered doses of neuromuscular blocking agents should be titrated to provide the optimum level of neuromuscular blockade (Grade of recommendation = C).

Monitoring

The Food and Drug Administration recommends the use of peripheral nerve stimulators in patients who are on NMBAs. It is critical to combine clinical monitoring with peripheral nerve stimulation to prevent the accumulation of the drug or its metabolites [41]. Some studies have compared clinical monitoring versus using peripheral nerve stimulation,

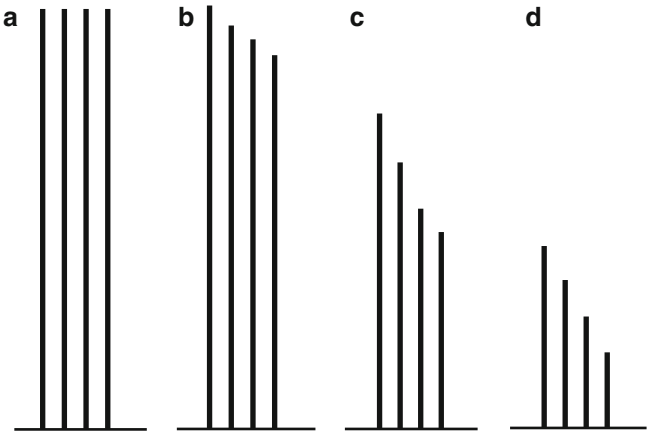


Fig. 5.13 Sequence of four supranormal stimuli at a frequency of 2 Hz during the train of four monitoring. The progressive decrease in responses (from the fourth stimulus to the first) was 0–75 % (**a**), 80 % (**b**), 85 % (**c**), 90–100 % (**d**) of receptor blockade, respectively. Therefore, (0) twitch = 100 % of blockade; (1) twitch = 90 % of blockade; (2) twitches = 85 % of blockade; (3) twitches = 80 % of blockade and (4) twitches = 0–75 % of blockade

showing that there was a need for smaller doses with peripheral nerve stimulation to achieve a better rate of neuromuscular function recovery [42, 43] and a lower hospital cost [44].

Peripheral nerve stimulation can give intensivists an estimation of the neuromuscular blockade magnitude, while the clinical assessment of muscle contraction is a subjective measure. The use of a force transducer provides a graphical representation and quantification of the response. Some tests have been previously described: single twitch, sustained tetanus, train-of-four, double-burst suppression and post-tetanic count. The most commonly used test is transcutaneous electrical stimulation of the ulnar nerve, using the train-of-four test. However, its implementation in young children can be a difficult procedure. Errors related to the system have been linked to electrical problems, such as low battery, inadequate current flow or poor wiring. Critically ill patients may have edema, sweating and very oily skin, which may interfere with electrode placement and the transmission of the electrical current. To perform the train-of-four test, a sequence of four supramaximal stimuli is performed at a frequency of 2 Hz at intervals of 0.5 s, leading to partial paralysis with a decline in the second, third and fourth twitches (Fig. 5.13).

Neuromuscular Blockade Reversal

Adequate neuromuscular blockade reversal is essential for restoring and maintaining laryngeal reflexes, respiratory effort and motor function [45]. This recovery may occur spontaneously and may be prevented by using agents that reverse the action of NMBAs, such as anticholinesterase drugs or cyclodextrins.

Anticholinesterases

Anticholinesterase drugs (0.07 mg/kg neostigmine, 0.5–1 mg/kg edrophonium or 0.2 mg/kg pyridostigmine) bind to the cholinesterase molecule and prevent the enzymatic catalysis of acetylcholine, with a consequent increase in its concentration. Neostigmine is the most commonly used drug for neuromuscular blockade reversal with non-depolarizing agents. Anticholinergic agents must always be pre-administered to prevent muscarinic side effects, such as 0.02 mg/kg atropine with a minimum dose of 0.15 mg or 0.01 mg/kg glycopyrrolate. Atropine has a faster action onset than glycopyrrolate. Approximately 50 % of neostigmine plasma clearance is dependent on renal excretion and the catalysis of plasma esterases [46]. Acetylcholinesterase inhibitors have disadvantages related to the slow antagonism of neuromuscular blockade or may be insufficient during deep blockade or in the presence of deep inhalation anesthesia.

Cyclodextrins

Cyclodextrins are new drug options that allow rapid control and the complete reversal of the neuromuscular blockade produced by NMBAs without the side effects of anticholinesterase drugs. A modified gamma-cyclodextrin, with a single and selective binding property (sugammadex), forms a firm, hydrophilic complex with steroidal NMBAs [47]. Sugammadex binds to rocuronium with a high affinity in a 1:1 complex. It also binds to vecuronium and pancuronium to a lesser extent. A study in pediatric patients has demonstrated that 2 mg/kg sugammadex is suitable in reversing the moderate neuromuscular blockade induced by rocuronium in infants, children and adolescents [48]. However, no other clinical studies to date have evaluated the effects of sugammadex in pediatrics/ neonatology. Sugammadex has an additional advantage, especially in the "cannot intubate, cannot ventilate" scenario in adult patients. It does not have many of the side effects related to anticholinesterase and cholinergic agents and can reverse a neuromuscular blockade of any depth when using rocuronium or vecuronium. Its limitations are related to cost and the inability to reverse non-aminosteroid agents [49].

Side Effects and Complications Following Long-Term Use

The occurrence of anaphylaxis with NMBAs is extremely rare; however, they have the potential for serious side effects, such as hypertension and prolonged paralysis. Cardiovascular effects are related to the stimulation or blockade of the autonomic nervous system and vasodilation

Table 5.3 Drugs and conditions that affect interaction with neuromuscular blocking agents

Enhance the effects	Antagonize the effects
Acidosis	Alkalosis
Aminoglycosides	Steroids
Other antibiotics (vancomycin, clindamycin, tetracycline, bacitracin, amphotericine B, polymyxin B)	Phenytoin
Calcium blockers	Carbamazepine
Beta-blockers	Theophylline
Antiarrhythmics (lidocaine, quinidine, procainamide, magnesium)	Sympathomimetic drugs
Chemotherapy (cyclophosphamide)	Childhood exposure to NMB agents
Dantrolene	Furosemide (1–4 mg/kg – dose related)
Local and inhaled anesthetics (isoflurane)	Hyper → K^+, Ca^{++}, thermia
Diuretics (thiazide and furosemide – low doses)	
Cyclosporine	
Neuromuscular diseases	
Hypo → K^+, Ca^{++}, Na^+, thermia	

Adapted from Grehn [64]. With permission from Wolters Kluwers Health

due to histamine release. Agents with a lower risk of cardiovascular complications are vecuronium, rocuronium and cisatracurium.

Several clinical factors may make reversal more difficult, including acid-base balance disorders [50], underlying neurological diseases [51], antibiotic use [52] and calcium channel blockers [53]. Table 5.3 lists some drugs and conditions that affect interaction with NMBAs.

Side effects can occur when using anticholinesterase drugs that act on both nicotinic and muscarinic receptors. The action of neostigmine may lead to severe bradycardia, an increased amount of secretions, increased gastrointestinal motility and bronchospasm [54]. Drugs with anti-muscarinic effects, commonly atropine or glycopyrrolate, administered simultaneously with anticholinesterase drugs may alter the parasympathetic control of heart rate, with decreased sensitivity of the baroreflex and heart rate variability [55]. A balance between the muscarinic effects of anticholinesterase drugs and the use of atropine or glycopyrrolate is not always achieved, which raises the possibility of changes in heart rate with neuromuscular blockade reversal [56].

Neuromuscular blockade complications in the ICU can be classified as short-term (accidental extubation, disconnection of the mechanical ventilator), medium-term (edema, venous thrombosis) and long-term (prolonged paralysis, muscle atrophy).

Critically ill patients receiving NMBAs for longer periods are at risk for developing profound motor weakness over a period of hours to months after discontinuing the medication, especially with the presence of other risk factors (e.g., corticosteroids, immobilization, severe sepsis or multiorgan failure and hyperglycemia) [57, 58]. The etiology of myopathy in severely ill patients is most likely multifactorial, and special care should be taken when co-administering NMBAs with corticosteroids to minimize the steroid dose and discontinue the use of NMBAs as soon as clinically possible. Myopathy should be suspected in severely ill patients with muscle weakness in the ICU [59].

It is important to note that even a minimal degree of muscle weakness due to NMBAs clinically alters the function of the upper and pulmonary airways [60]. In 2006, Testelmans D et al. [61] performed an analysis of muscle weakness in rats and reported a decrease in diaphragmatic strength in animals subjected to mechanical ventilation after the infusion of rocuronium for 24 h. However, a recent study [62] concluded that NMBAs have a significant additive effect on diaphragmatic muscle weakness, suggesting that mechanical ventilation and sedation are the factors that trigger diaphragm weakness in ICU patients. Monitoring the neuromuscular blockade depth (clinical examination and peripheral nerve stimulation) is recommended and allows the use of lower doses of NMBAs, which may minimize these side effects [63].

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Procedural Sedation and Anesthesia in the PICU

6

Stephen D. Playfor and Katherine Kirkpatrick

Abstract

Critically ill children in the Pediatric Intensive Care Unit (PICU) frequently undergo painful and anxiety-provoking procedures as part of their overall evaluation and management; these may include central line insertion, arterial line placement, chest tube placement, and lumbar puncture. Recently there has been a growing trend towards performing elective diagnostic and therapeutic procedures in children, which formerly required hospitalization, as same-day ambulatory procedures. Procedural sedation is often utilized to facilitate the safe and successful performance of these ambulatory procedures in children, in order to minimize complications and decrease the pain and anxiety associated with them.

Prior to the administration of procedural sedation it is important that adequate preparation has taken place in order to maximize patient safety. Preparation should include a full health evaluation noting the fasting status, performance of a guided risk assessment, assignment of a physical status score, and the generation of a sedation plan. Minimum monitoring standards should be maintained from the administration of sedative agents until the recovery criteria are met.

Non-pharmacological measures can be very useful in alleviating anxiety on the part of the patient and may reduce the need for pharmacological agents. Massage, music, video-viewing, nursery rhymes and story telling are all techniques frequently employed on the PICU during painful procedures.

Pharmacological agents commonly used to facilitate procedural sedation include chloral hydrate, benzodiazepines such as midazolam, ketamine and propofol.

Keywords

Sedation • Procedures • Midazolam • Ketamine • Propofol

Introduction

Critically ill children in the Pediatric Intensive Care Unit (PICU) frequently undergo painful and anxiety-provoking procedures as part of their overall evaluation and management, including central line placement, arterial line placement, chest tube placement, and lumbar puncture. Recent years have witnessed a growing trend towards performing elective diagnostic and therapeutic procedures in children, which formerly required hospitalization, as same day ambulatory procedures. Studies show that children who undergo these diagnostic and therapeutic procedures often find the actual procedure to be

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worse than their disease [1, 2]. Procedural sedation is often utilized to facilitate the safe and successful performance of medical procedures in children, as well as to minimize complications and decrease the pain and anxiety associated with these procedures. Many hospitals have created pediatric sedation centers designed especially for this purpose, while other hospitals use the PICU to perform these 'outpatient' medical procedures. The Pediatric Intensivist therefore frequently provides procedural sedation and anesthesia in a number of different circumstances in the PICU, as well as in non-critically ill children from a variety of other settings.

Definition of Procedural Sedation

There is considerable variation in the definition of the target states for procedural sedation. Some of the most commonly referred to are those of the American Academy of Pediatrics (AAP) originally produced in 1992, with revisions in 2002 and 2006 [3–5]. Recent efforts have been aimed at coordinating a unified nomenclature and common standards for pediatric procedural sedation. The aims of procedural sedation in children are generally to allow the completion of a specific procedure with relief of anxiety and pain and reduction of excessive movement using therapeutic agents appropriate to the clinical circumstance. Current definitions describe a continuum of the depth of sedation ranging from 'minimal sedation' (formerly anxiolysis), through 'moderate sedation' (formerly conscious sedation or sedation/analgesia) and 'deep sedation' (formerly deep sedation/analgesia) to 'general anesthesia' [6]. *Minimal sedation* is defined as a drug-induced state during which patients respond normally to verbal commands, although with impaired cognitive function and coordination and where ventilatory and cardiovascular functions remain unaffected. *Moderate sedation* is defined as a drug-induced depression of consciousness during which patients respond purposefully to verbal commands (e.g. open your eyes), which may be accompanied by gentle tactile stimulation. No interventions are required to maintain a patent airway, spontaneous ventilation is adequate, and cardiovascular function is usually maintained. *Deep sedation* is defined as a drug-induced depression of consciousness during which patients cannot be easily roused but will respond purposefully following repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired, spontaneous ventilation may be inadequate, and the patient may require assistance in maintaining a patent airway. Protective airway reflexes may be lost, though cardiovascular function is usually maintained. *General anesthesia* is defined as a drug-induced loss of consciousness during which patients are not arousable. The ability to maintain a patent airway and spontaneous respiration is depressed and the patient may require ventilatory support. Cardiovascular function may also be impaired. A state of "dissociative sedation" has also been defined when referring to the effects of ketamine (see below). These various target states require various safety nets to ensure that adverse effects are avoided or minimized and that a child can be rescued promptly and safely should an adverse effect occur.

Table 6.1 American Society of Anesthesiologists (ASA) Physical Status Score

ASA physical status	Description
Class I	Healthy child
Class II	Child with mild systemic disease that does not limit normal activity
Class III	Child with severe systemic disease that limits normal activity
Class IV	Child with severe systemic disease that is a constant threat to life
Class V	Moribund child not expected to survive without surgery

Note: Generally, children meeting criteria for ASA Physical Status Class III, IV, or V are not suitable candidates for procedural sedation, and in these cases, general anesthesia is preferable

Preparation for Sedation

Pre-procedural Assessment

For elective procedures appropriate informed consent should be obtained and documented in the patient's medical record [7]. This should be obtained by the person responsible for administering the sedation. In an emergency it is justifiable to proceed without informed consent if it is vital to the child's wellbeing [6]. However, in most cases of procedural sedation, there will be ample time to obtain written, informed consent. A full health evaluation should be carried out prior to sedation. Conducting a pre-sedation assessment can reduce the incidence of complications during procedural sedation in children. Such an assessment should include noting the fasting status, performance of a guided risk assessment, assignment of a physical status score (Table 6.1), and generation of a sedation plan. Hoffman and colleagues found that adherence to guidelines for a structured process for pediatric procedural sedation reduced the occurrence of adverse events [8]. Assessment of the airway for history or features which may increase risk of sedation should also form part of the pre-sedation assessment. Vespasiano and colleagues found that development of a pre-procedural airway score assisted in identifying patients who may need airway interventions which may aid formulation of the sedation plan [9].

Table 6.2 NPO guidelines

Infants 0–5 months of age	No milk or solids for 4 h before procedure
Infants 6–36 months of age	No milk or solids for 6 h before procedure
Children > 36 months of age	No milk or solids for 8 h before procedure

Note: Clear liquids are acceptable up to 2 h before procedure

Fasting Guidelines

As sedation may cause depression of protective airway reflexes it is generally recommended that children receiving sedation for elective procedures undergo the same pre-procedural preparation with regards to fasting as for in preparation of general anesthesia. Therefore children should not drink fluids or eat solid foods for a sufficient period of time to allow for gastric emptying prior to their procedure; this would equate to 2 h for clear fluids, 4 h for breast milk and 6 h for formula milks and solid food (Table 6.2). However this recommendation is controversial and there is evidence to suggest pre-procedural fasting may not be necessary. In addition prolonged fasting may lead to hypoglycemia in young infants. Agrawal and colleagues studied 1,014 patients undergoing procedural sedation and analgesia in the Emergency Department where 56 % were not fasted in accordance with established guidelines [10]. Emesis occurred in 15 patients (1.5 %) with no documented episodes of aspiration, and there were no significant differences in the median fasting duration between patients with and without adverse events and between patients with and without emesis. Similarly, Roback and colleagues studied 2,085 patients receiving parenteral sedation by emergency physicians for procedures [11]. Emesis occurred in 156 patients (7.5 %) with no episodes of aspiration. Again there was no association found between pre-procedural fasting and the incidence of adverse events. A further study by Bell in 2007 of 400 patients receiving propofol for sedation in the emergency department found 70 % of patients were not fasted and reported no cases of aspiration or adverse events [12]. These and other data have been used to argue that fasting is not needed prior to procedural sedation, though most practitioners agree that this depends on the target state, patient, procedure and drugs to be used. In 2010 a large systematic review on pre-procedural fasting in the emergency department concluded that high level evidence suggests there is no link between non-fasted patients and pulmonary aspiration therefore strict adherence to fasting guidelines may be unnecessary [13]. However it is worth considering that some patient groups are at higher risk of aspiration; for example trauma patients and those with gastro-oesophageal reflux, therefore it is worth considering fasting period as part of the pre-procedural assessment and creation of a sedation plan.

Monitoring

Minimum monitoring standards should be maintained from the administration of sedative agents until the recovery criteria are met, which should all be documented within the patient's notes. This should include level of sedation, details of drugs administered, assessment of ventilatory status, pulse rate, non-invasive blood pressure and any adverse incidents. Ventilatory status should be monitored by means of observation or auscultation and with the use of pulse oximetry or ideally capnography. Pulse oximetry is not a good measure of hypoventilation in the presence of supplemental oxygen. Deitch and colleagues reported that the addition of capnography to standard monitoring reduced incidents of hypoxia in adults receiving sedation in the emergency department [14]. Similar results were reported by Lightdale and colleagues in a study of 163 children undergoing sedation for gastrointestinal procedures as part of a randomized controlled trial. Use of capnography increased detection of alveolar hypoventilation and reduced hypoxemic events [15].

Monitoring of the level of consciousness of those undergoing procedural sedation allows for the titration of sedative agents in order to achieve the target depth of sedation. Maintenance of verbal contact or responsiveness to light tactile stimulation are useful for the lighter planes of sedation, but are not so useful for younger pre-verbal children, when stimulation of the child might interfere with the procedure, (for example during diagnostic imaging) or when dissociative sedation is being used. Some authors have advocated the use of the bispectral index monitor as a quantitative scoring system for use during procedural sedation [16, 17]. The bispectral index (BIS) is a processed neurophysiological electroencephalographic parameter which may be used for evaluating the depth of sedation or anesthesia in the critically ill. Although the BIS monitor correlates well with clinical measures of deeper levels of hypnosis, sedation, and anesthesia, it is a poor predictor of movement in response to painful stimuli and is not a good measure of the adequacy of analgesia. The BIS monitor does not work for ketamine dissociative sedation as the value increases rather than falls as more drug is administered. The resolution of BIS is poor when trying to differentiate lighter levels of sedation. There is currently insufficient evidence to recommend the routine use of BIS monitors during procedural sedation.

It is good practice for a specific individual, other than the operator carrying out the procedure, to monitor the patient throughout any procedure performed under sedation. This

Table 6.3 Suggested emergency drugs

Oxygen
Glucose (D50W)
Atropine
Epinephrine (1:1,000 and 1:10,000)
Phenylephrine
Dopamine
Diazepam
Isoproterenol
Calcium chloride or calcium gluconate
Sodium bicarbonate
Lidocaine (both for resuscitation and local anesthesia)
Naloxone hydrochloride
Diphenhydramine hydrochloride
Hydrocortisone
Methylprednisolone
Succinylcholine
Aminophylline
Racemic epinephrine
Albuterol by inhalation

Adapted from Refs. [3, 4]
Note: The choice of emergency drugs may vary according to individual need and local practices

Table 6.4 Suggested emergency equipment

Airway and breathing
Face masks (Infant, child, small adult, medium adult, large adult)
Breathing bag and valve set
Oral airways (Infant, child, small adult, medium adult, large adult)
Nasal airways (Small, medium, large)
Laryngoscope handles
Laryngoscope blades
Straight (Miller) No. 1, 2, 3
Curved (Macintosh) No. 2, 3
Endotracheal tubes
2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 uncuffed
6.0, 7.0, 8.0 cuffed
Stylettes (appropriate sizes for endotracheal tubes)
Surgical lubricant
Suction catheters (appropriate sizes for endotracheal tubes)
Nasogastric tubes
Yankauer-type suction catheter
Portable nebulizer
Circulation
Intravenous catheters (24-, 22-, 20-, 18-, and 16-gauge)
Tourniquets
Alcohol wipes
Adhesive tape
Assorted syringes (1, 3, 6, and 12 mL)
Intravenous tubing
Pediatric drip (60 drops/ml)
Pediatric burette type
Adult drip (10 drops/ml)
Extension tubing
Intravenous fluid
Lactated Ringer's solution
Normal saline
Three-way stopcocks
Pediatric intravenous (IV) boards
Intraosseous bone marrow needle
Sterile gauze pads
Gloves

Adapted from Refs. [3, 4]

individual should be trained in the recognition of complications associated with the administration of sedative and analgesic agents and should be trained in basic life support skills when moderate sedation is planned, and trained in advanced life support skills whenever deep sedation is planned. Because sedation is a continuum from anxiolysis through to general anesthesia, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation inadvertently becomes deeper than that initially intended. A full range of age-appropriate emergency equipment should be available whenever sedative or analgesic drugs capable of causing cardiorespiratory depression are administered (Tables 6.3 and 6.4). Specific antagonists should be available for opioid agents (naloxone) and benzodiazepines (flumazenil).

Patients may continue to be at risk of developing complications after the completion of procedures performed under sedation especially if routes other than the intravenous one are used for the administration of sedative agents. Units should therefore develop clinical guidelines for the recovery and discharge of these patients. The patient should be observed in a suitably equipped recovery area with appropriately trained staff for continued monitoring of the patients respiratory and cardiovascular parameters until recovery criteria are met (Table 6.5). In the large prospective study published by the Pediatric Sedation Research Consortium data from 114,855 subjects were collected and analyzed. There was significant variation in the frequency of use of each physiologic monitoring modality with the largest difference in frequency of monitoring use being seen between providers using electrocardiography; which varied from 13 to 95 % [18].

Complications

The true complication rate of procedural sedation is difficult to define. Some authors seem to suggest that any sedation regimen that allows a procedure to be completed is successful. Clearly the goals of procedural sedation vary according to the clinical setting and while a prolonged recovery time after a specific procedure may have no bearing on a critically ill, mechanically ventilated child, it may be a significant factor

Table 6.5 Recommended discharge criteria

Generally, once all of the following criteria have been met, a child is ready for discharge:

1. Cardiovascular function and airway patency are satisfactory and stable
2. The patient is easily arousable, and protective reflexes are intact
3. The patient can talk (if age-appropriate)
4. The patient can sit up unaided (if age-appropriate)
5. For a very young or handicapped child, incapable of the usually expected responses, the presedation level of responsiveness or a level as close as possible to the normal level for that child should be achieved
6. The state of hydration is adequate

in the management of an out-patient undergoing the same procedure. This may explain why the reported rates of failure of procedural sedation vary so widely from 1–3 % up to 10–20 % [19].

Cote and colleagues reported that adverse sedation events were not particularly associated with one specific class of sedative agent but were commonly associated with drug overdosing and when multiple agents were used, particularly three or more agents [20]. Cote has also demonstrated that adverse outcomes after procedural sedation occur more commonly in the non-hospital setting where there is also a greater chance of inadequate resuscitation [21]. The complication rate during procedural sedation also increases with the depth of sedation. Hoffman and colleagues reported complications in 34 patients out of 895 (3.8 %) undergoing planned 'conscious' sedation and in 6 patients out of 65 (9.2 %) undergoing planned 'deep' sedation [8]. Caperell and Pitetti reported a higher adverse event rate in those patients ASA class 2 and above from a study of 1,232 patient receiving procedural sedation in the emergency department [22].

Sedation Strategies

Non-pharmacological Measures

Non-pharmacological measures can be very useful in alleviating anxiety on the part of the patient and reduce the need for pharmacological agents. Massage, music, video-viewing, nursery rhymes and story telling are all techniques frequently employed on the PICU during painful procedures [23–25]. Guided imagery is particularly useful in young school age children. Communication of procedural information [26], continual reorientation, reassurance, environmental noise reduction and the presence of relatives at the bedside can all allay anxiety. A Cochrane review reported some evidence that cognitive behavioral interventions can reduce the pain and distress in painful procedures [27]. New developments using virtual reality technology have been developed and used with some success to alleviate distress from painful procedures [28].

Pharmacological Agents

Chloral Hydrate

This venerable hypnotic agent is still frequently used, particularly prior to diagnostic imaging in children under 3 years of age (Table 6.6). It is converted to trichloroethanol and has no analgesic properties. The most common adverse events associated with chloral hydrate are gastrointestinal intolerance, myocardial depression, hypotension and arrhythmias. Triclofos sodium is a chloral hydrate derivative which causes fewer gastro-intestinal disturbances. Paradoxical excitement/agitation may occur, and in combination with other sedative agents respiratory depression may be profound. Although traditionally thought of as a safe drug with predictable effects and minimal respiratory depression, Cote and colleagues found that chloral hydrate was the most common drug whose administration as a single sedative agent resulted in death or permanent neurological injury [20]. Similarly, Hoffman reported that chloral hydrate was the only agent whose use was associated with higher risk of adverse events even when used as the sole sedative agent and after adjusting for target sedation level [8]. It was the only agent in this study to be associated with the inadvertent development of deep sedation when used alone.

Chloral hydrate can have a long half life which varies from 4 to 12 h; as such it may not be the most logical choice of sedative agent for brief procedures in patients who are not mechanically ventilated. Importantly there is also a significant incidence of prolonged recovery and delayed side effects with chloral hydrate [29]. These investigators found restlessness and agitation lasting more than 6 h in around 30 % of children undergoing neuroimaging with chloral hydrate sedation, 5 % of whom did not return to normal for 2 days after the procedure. An additional consideration is that the chloral hydrate is no longer commercially available in the United States, though some hospitals are compounding it themselves.

Benzodiazepines

Midazolam is the most commonly used sedative agent for procedural sedation in children and adults. Midazolam's imidazole ring provides stability in solution and allows for rapid metabolism with midazolam having the most rapid clearance of the commonly used benzodiazepines. Benzodiazepines exert their effects through the $GABA_A$ receptor and midazolam provides potent sedation, antegrade amnesia, and anxiolysis. Importantly the effects of midazolam can be reversed with the antagonist flumazenil.

Table 6.6 Commonly used sedative agents for procedural sedation

Agent	Route of administration	Onset of action (min)	Duration of action	Dose range commonly cited	Major adverse effects
Chloral hydrate	PO, PR	30–40	0–90 min	60–80 mg/kg	Slow, unpredictable onset Long, irreversible duration Paradoxical agitation Nausea/vomiting
Midazolam	PO	20–30	30–60 min	0.2–0.6 mg/kg	Respiratory depression Hypotension
	PR	20–30	30–60 min	0.2–0.6 mg/kg	
	IN, SL	3–5	30–60 min	0.2–0.3 mg/kg	
	IM	1–5	30–60 min	0.05–0.1 mg/kg	
	IV	1–5	15–30 min	0.05–0.1 mg/kg	
Pentobarbital	IM	10–15	15–30 min	2–6 mg/kg	Respiratory depression
	IV	<1	15 min	1–3 mg/kg	
	PO	15–60	1–4 h	2–6 mg/kg	Hypotension
Ketamine	IM	5–10	3–4 h	3–4 mg/kg	Emergence dysphoria, agitation
	IV	1–5	1–2 h	1–2 mg/kg	Hypersalivation
Propofol	IV	10–15	5–10 min	1–2 mg/kg induction	Respiratory depression
				150–250 μg/kg/min (continuous infusion)	Hypotension
Remifentanil	IV	1–3	5–10 min	1 μg/kg bolus	Respiratory depression
				0.25–1 μg/kg/min (continuous infusion)	Hypotension Nausea/vomiting
Dexmedetomidine	IV	30		1 μg/kg bolus (over 10 min)	Bradycardia
				0.2–0.7 μg/kg/h (continuous infusion)	Hypertension

IN intranasal administration, *SL* sublingual administration

The metabolism of midazolam can be impaired by concurrent administration of macrolide antibiotics or grapefruit juice which causes significant prolongation of its sedative effects.

Midazolam can be administered by multiple routes; intravenous, oral and intranasal. Intranasal is advantageous as it can be used the combative child with no intravenous access, although it can cause nasal irritation on administration as the soluble formulation has an acidic pH. In a study by Wood and colleagues only 57 % of patients found it acceptable [30] although it can be combined with lignocaine to reduce nasal discomfort [31].

In a prospective study of 561 patients by Singh and Kumar intravenous midazolam was found to be an effective sole agent for sedation for CT scan with a failure rate of 2.11 % with no respiratory depression requiring intervention more than application of oxygen [32]. However midazolam has no analgesic properties and may not be as effective as sole agent for painful procedures.

Propofol

Propofol (2,6-diisopropylphenol) is an intravenous sedative-hypnotic agent used in the induction and maintenance of anesthesia in adults and children over the age of 1 month, and for the sedation of adults during critical illness. It is unrelated to barbiturate, steroid, imidazole or eugenol drugs. One of the most attractive properties of the agent is its rapid onset of action; hypnosis usually occurring within 40 s from the start of an injection. It is rapidly taken up into brain tissue and works through a variety of mechanisms. The drug appears to work, at least partially, through the $GABA_A$ receptor pathway, in that it potentiates $GABA_A$-evoked responses and probably also activates the $GABA_A$ receptor complex directly. A further appealing property of propofol is its very rapid recovery time once the drug is discontinued.

In 2001 the UK Medicines Control Agency and Committee on Safety of Medicines repeated advice that propofol was contraindicated in children aged 16 years and under when used as an infusion for sedation and was not recommended for procedural sedation in children [33]. The reason for caution in the administration of propofol for sedation is that it has been associated *during prolonged administration* with the so-called propofol infusion syndrome characterized by acidosis, bradyarrhythmia and rhabdomyolysis. This complication is rare but frequently fatal and has been reported in some 21 children and 14 adults [34]. At the subcellular level, propofol impairs fatty acid oxidation and mitochondrial activity with transient elevations in malonylcarnitine and C5-acylcarnitine during propofol infusion syndrome [35].

A survey of PICUs in the UK and North America in 2004 found propofol was used for sedation during procedures by all 48 responding units. Amongst the UK units 35 % reported that they would be less likely to use propofol for procedures than in the past, compared to 18 % of North American Units [36]. A survey of UK PICUs in 2007 reported propofol use in only 2.6 % patients but reported no adverse incidence associated with use of propofol [37].

Pediatric Sedation Research Consortium reported a serious complication rate of 2.28 %; (95 % confidence interval 2.1–2.5 %) from 25,433 pediatric propofol sedations by emergency physicians. This included only one cardiac arrest, one emergency intubation and two cases of aspiration [38]. Similar low respiratory complication rates were reported by Machata following a propofol sedation regime for 500 patients undergoing for MRI scanning [39].

Vespasiano and colleagues studied Intensivists' experience of 7,304 propofol sedations in patients ranging from 1 month to 21 years. They found propofol had an acceptable safety profile with no procedures abandoned; 5 % of patients suffered brief rapidly correctable desaturation, 2.6 % patients required some form of airway or respiratory intervention and severe airway incidences such as laryngospasm and aspiration were rare (0.27 %, 0.01 %). Hypotension was relatively common (31 %) but requirements of greater than 40 ml/kg volume replacement was unusual (0.11 %) [40].

Reeves and colleagues studied 16 children who underwent 19 intrathecal chemotherapy and bone marrow aspirations. The children were monitored with BIS scores and the lowest mean BIS score for all of patients was 29.7 ± 13.7, indicating that a depth of sedation equivalent to general anesthesia was necessary to allow the practitioner to perform the procedure [41]. Given the depth of sedation that appears to be produced when using propofol for procedural sedation it is not surprising that a relatively high rate of minor airway compromise and is reportedly associated with its use [42, 43]. Despite these reservations propofol has been safely used in large cohorts of children, even for prolonged sedation, and administered by non-anesthesiologists [44].

Ketamine

Ketamine is a dissociative anesthetic agent, structurally similar to phencyclidine, which produces a cataleptic trance-like state by apparently producing an electrophysiological dissociation between the limbic and thalamoneocortical systems [45]. It is the only agent that confers high levels of both sedation and analgesia. It has a rapid onset of action and a short duration of action owing to its short redistribution half-life of 5 min; the elimination half-life is 130 min. Ketamine has several unique features that include producing virtually no central respiratory depression, the maintenance of airway reflexes, and bronchodilation. In addition, functional residual capacity, minute ventilation and tidal volume are unaffected following the administration of ketamine. It has fewer cardiac side effects than other sedative agents primarily because it stimulates endogenous catecholamine release, producing increases in heart rate, blood pressure and cardiac output. Ketamine may have a particular role for emergency procedures where patients have not been fasted. In 30 years of regular use, there have been no documented reports of clinically significant aspiration of gastric contents following the use of ketamine for procedural sedation in patients without established contraindications. Early reports suggested that the administration of ketamine to patients with evolving intracranial processes was associated with clinically important increases in intracranial pressure [46]. More recent data suggest that these increases are more modest and may be blunted by pre-treatment with benzodiazepines [47].

Green and colleagues reported a retrospective study of 442 procedural sedation episodes using ketamine in 333 children on a PICU [48]. Adequate sedation was noted in all but nine procedures (98 %). Complications were understandably more common in those children who were not already intubated with 15 airway complications (5.4 %) and ten episodes of emesis (3.6 %) in non-intubated patients. Ketamine may be administered intravenously or intramuscularly however Melendez and Bachur reported that although serious adverse incident rate using ketamine was low (1 %); higher rates were seen in patients receiving intramuscular drug (odds ratio 2.1, 95 % CI, 1.3–3) most noticeably increased incidence of laryngospasm [49].

Ketamine is increasingly being used in combination with propofol; which has been referred to as "ketofol". Several studies have shown this combination to be effective whilst having a favorable side effects profile by combinations of their clinical actions [50, 51]. David and Shipp, however, reported no difference in the incidence of respiratory depression in a comparison between "ketofol" and propofol alone [52].

Barbiturates

Barbiturates have been used for many years to provide procedural sedation in children and are frequently the agents of choice to facilitate diagnostic imaging in children aged 3 years and older. They have the advantage that they can be delivered by multiple routes. Pentobarbital has been reported to produces successful procedural sedation in 98 % of children undergoing diagnostic imaging. In a recent study however, pentobarbital facilitated a quicker sedation onset and reduced the requirement for supplemental sedation compared to chloral hydrate, but produced a higher incidence of paradoxical reaction (14 %) and prolonged recovery [53].

Remifentanil

Remifentanil is an ultra-short acting opioid agent metabolized by plasma and tissue esterases and is characterized by having a very short context-sensitive half life. When used in

17 children for sedation during painful procedures, Bauman and colleagues found an unacceptably high incidence of life-threatening respiratory depression at subtherapeutic levels of the drug [54]. This feature may makes remifentanil more useful in situations where the airway is already protected, either in the mechanically ventilated PICU patient or during procedures such as fiberoptic bronchoscopy. Berkenbosch and colleagues reported on the use of remifentanil during flexible fiberoptic bronchoscopy in 15 pediatric patients. All procedures were completed easily without significant complications being reported. Patients recovered to baseline status 13.3 min (±8.5 min) following discontinuation of the infusion [55]. Similarly, Reyle-Hahn studied the use of a continuous infusion of remifentanil and intermittent boluses of propofol for sedation during flexible fiberoptic bronchoscopy in 26 children. Sedation was successfully achieved in all children without any adverse effects being reported. Here, all patients were awake at 5 min (±1.3 min) following discontinuation of the remifentanil infusion [56].

Dexmedetomidine

Dexmedetomidine is a potent alpha-2-agonist which has become popular due to its favorable side effects profile. Dexmedetomidine is currently only licensed for short-term sedation in adult patients and does not yet have approval for use in children despite evidence to support its use in the literature. Dexmedetomidine acts via activation of presynaptic alpha-2-receptors; which centrally causes reduced sympathetic activity and spinal action causes potent analgesia [57]. Dexmedetomidine is administered by intravenous bolus followed by an infusion, although there have been limited reports of use via the oral route [58]. Initial reports suggested that dexmedetomidine may not suitable to be used as a sole agent and has been used in combination with midazolam and ketamine [59–61]. However, Mason et al. reported a 97.6 % success rate when used as a sole agent for MRI scan [62]. Dexmedetomidine has also been used successfully to prevent emergence delirium and withdrawal when recovering from sedation from other agents [63, 64].

Dexmedetomidine appears to have to minimal respiratory effects even at high doses [65] making it an ideal agent for sedation. The main adverse effects seen are cardiovascular and easily correctable by cessation of the infusion [59]. Hammer et al. conducted electrophysiological studies on patients receiving dexmedetomidine sedation for cardiac ablation and reported significant sinoatrial and atrioventricular node depression causing significant bradycardia and hypertension [66]. However two studies by Mason et al. reported hypertension in only 4.9 % of patients and bradycardia in 16 % with no adverse sequelae in patients receiving high-dose dexmedetomidine infusion for imaging. The incidence of hypertension appears to be higher if the patient is less than 1 year of age [67, 68].

Inhalational Agents

Inhalational agents have been used for procedural sedation and have the advantage of not requiring intravenous access. Nitrous oxide has analgesic, amnesic and anxiolytic properties and induces a dissociative sedation. The PediSedate® is a nitrous oxide delivery system with a headset which can be combined to an interactive video game as a distraction therapy. Brown et al. reported with use of the PediSedate® compared to a standard care regimen reduced significantly less distress and improved patient cooperation [69]. The AAP had cautioned against nitrous oxide concentration greater than 50 % due to increased likelihood of moderate or deep sedation [5]. Zier and colleagues however reported a significant number of children remain minimally sedated while receiving N_2O at concentrations greater than 50 % via a hood system and no difference in the incidence of adverse events than those receiving less than 50 % in study of 1858 cases [70].

Sevoflurane has been found to be effective sedative for outpatient gastrointestinal endoscopy. Montes and Bohn found that compared to combined midazolam-fentany- ketamine sevoflurane was associated with lower incidence of adverse effects and decreased time to wakening and discharge [71]. However the use of anaesthetic agents requires specialist delivery systems and knowledge.

Comparative Studies

Comparative studies of sedative agents for procedures in PICU are hampered by the low incidence of serious adverse events. Many thousands of patients would need to be enrolled in prospective studies to establish any difference in mortality between two different regimes. Several authors have compared propofol with ketamine for procedural sedation. Vardi and colleagues studied 98 children who underwent 105 procedures using propofol sedation for 58 procedures, and ketamine with midazolam and fentanyl for 47 procedures [43]. Both protocols provided effective sedation. Recovery time was significantly shorter in the propofol group (23 min vs 50 min) although transient decreases in blood pressure, partial airway obstruction, and apnea were more frequent in this group. Five children (10.6 %) who had received ketamine experienced discomfort during emergence from sedation. The authors highlight that because transient respiratory depression and hypotension are associated with propofol administration, it should only be used in a monitored environment under the supervision of suitably trained staff.

Seigler and colleagues concluded that both propofol and ketamine combined with midazolam provided adequate sedation for most pediatric procedures but that the mean time to awakening was significantly less with propofol than when ketamine was used (36.6 ± 15 min Vs 69.2 ± 43 min) [41].

The rate of unplanned tracheal intubation was the same in both groups at 0.7 %. More minor complications were reported with propofol, but all responded to airway repositioning, supplementary oxygen and intravenous fluid administration. Similar results were reported by Lebovic and colleagues who compared propofol with ketamine in 20 pediatric patients undergoing cardiac catheterization [72]. Seven patients in the propofol group experienced a transient decrease in mean arterial blood pressure of greater than 20 % of baseline compared to only one patient in the ketamine group. Time to full recovery was significantly less in the propofol group (24 ± 19 min Vs 139 ± 87 min).

Mallory and colleagues compared propofol and pentobarbitone sedation in 11,846 patients undergoing MRI scan (propofol: n = 5072, pentobarbitone: n = 2007) concluding that propofol was more effective. Pentobarbitone had increased incidence of procedure cancellation due to poor sedation, vomiting, unplanned admission and allergic complications. There was significant difference in the incidence of airway complication and recovery time for propofol was significantly shorter (30 v 45 min) [73].

Kennedy and colleagues studied 260 children requiring emergency fracture or joint reduction who received intravenous midazolam plus either fentanyl or ketamine [74]. Both regimens were effective in facilitating fracture reduction ketamine proved more effective than fentanyl for relief of pain and anxiety in children. Respiratory complications occurred less frequently with ketamine than with fentanyl, but respiratory support was required by children receiving both protocols. The average time required for recovery was longer for ketamine/midazolam than for fentanyl/midazolam (127.6 ± 56.2 min Vs 113.3 ± 36.9 min).

Safety of the Clinical Setting

It is important to emphasize that the standards of sedation practice outside the PICU setting should be the same as within the PICU. This is particularly important where advanced techniques are used, when drug combinations are employed, and when younger or less fit patients are to be sedated. In many cases the standards must be equivalent to those for children undergoing general anesthesia.

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Blood Conservation in the Perioperative Setting

7

B. Craig Weldon

Abstract

Children undergoing high blood loss surgical procedures face the same risks associated with transfusion as adults but must live with the sequelae of transfusion-related complications throughout a much longer life span. Avoidance of allogeneic blood transfusion can be accomplished with a team approach that relies on a thorough understanding of patient- and procedure-associated risk factors for bleeding, allowing patients who might benefit from a perioperative blood conservation strategy to be identified. The individual components of a multidisciplinary, multimodal blood conservation plan are discussed in this chapter. These elements include preoperative erythropoietin therapy, perioperative autologous blood collection (preoperative autologous donation, intraoperative hemodilution and cell salvage), antifibrinolytics, deliberate hypotension, and blood sparing surgical techniques. The adoption of lower transfusion triggers, institutional transfusion algorithms, and reduced blood sampling can result in fewer transfusions for all pediatric surgical patients.

Keywords

Blood conservation • Blood transfusion, allogeneic • Blood loss, surgical • Blood transfusion, autologous • Antifibrinolytic • Hemodilution • Transfusion triggers • Transfusion, risks

Introduction

The appearance of the acquired immunodeficiency syndrome (AIDS) and the attendant risk of transmission of its agent, the human immunodeficiency virus (HIV), through blood products prompted a massive effort to lower transfusion rates around the world. While the infectious risks of transfusion have been nearly eliminated through better donor screening, collection processes and testing, continued concerns about the noninfectious risks of transfusion mandate the avoidance of allogeneic transfusions whenever possible. Given that surgical patients are the biggest consumers of blood, and intraoperative transfusion can have major impacts on mortality and morbidity [1], perioperative blood conservation has become an imperative. This chapter will provide the justification for avoiding allogeneic blood transfusion (ABT) in the perioperative setting, a discussion of high risk of transfusion scenarios, and an overview of currently accepted methods of blood conservation in the pediatric surgical population.

Risks of Transfusion and the Need for Blood Conservation

A recent review compiled the estimated risks of transmitting hepatitis B, hepatitis C, HIV, and human T-lymphotrophic virus based on data from hemovigilance systems in the U.S., U.K. and Canada [2]. The extremely low risk of transfusion-associated HIV from the US data (1 in 1.5 billion donations)

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is due to careful donor screening and nucleic acid testing for viral contamination. Unfortunately, there continue to be constant threats to the blood supply from emerging new infectious agents, such as the recent appearance of West Nile Virus and the prion responsible for variant Creutzfeld-Jakob disease. Other blood-borne agents are expected to emerge over the coming years due to globalization, climate change, and other factors. Due to improved collection, processing and detection practices, bacterial contamination of blood and platelets is decreasing but still remains problematic, accounting for 10 % of U.S. and U.K. transfusion-related fatalities [3].

The non-infectious risks of transfusion have been recognized for years (acute hemolytic reactions, alloimmunization, post-transfusion purpura, anaphylaxis, febrile reactions, graft versus host disease, and circulatory overload). However, Transfusion Related Acute Lung Injury (TRALI) [4] and Transfusion Related Immunomodulation (TRIM) [5] have only recently become fully appreciated as complications of blood product administration. The clinical presentation of TRALI (new onset, hypoxemic pulmonary dysfunction within 6 h of a transfusion) is thought to be under recognized but is responsible for at least a third of transfusion-related deaths in the U.S. and Great Britain [3]. Reports of TRALI in pediatric patients [6] are uncommon, likely a reflection of the difficulty in establishing the diagnosis and the lack of pediatric practitioners' familiarity with this entity. The clinical effects of TRIM are even more obscure than TRALI and appear to be, in part, a consequence of the red blood cell "storage lesion". The often reported association between the perioperative transfusion of "old" red blood cells (RBC) and the progression of cancer [7] and postoperative infections and mortality [8] has yet to lead to a cohesive mechanistic explanation of TRIM. Myriad other elements of the storage lesion such as decreased RBC deformability [9], changes in microvascular blood flow [10, 11], reduced oxygen delivery to tissues [12], and organ dysfunction [13] are also under active investigation. Interestingly, a 2010 analysis of over 400,000 transfusion episodes on the effects of duration of RBC storage found minimal association between the age of transfused RBCs and post-transfusion mortality [14].

Data from the United Kingdom's transfusion auditing system, Serious Hazards of Transfusion (SHOT), show that the overall incidence of adverse transfusion reactions in infants and children exceeds that of adult patients [15]. Eighty-two percent of the incidents reported to SHOT involved errors in physician prescribing, laboratory or blood bank procedures, and/or administration of the blood product. These "clerical" (or mistransfusion) errors were more common in children, reflecting the more complex, specialized transfusion needs of this population [15].

There are societal arguments for perioperative blood conservation when one considers the potential cost savings [16, 17] and the fact that our increasingly elderly population undergoes the majority of surgical procedures that require blood administration. The current donor pool will shrink as older individuals will not be able to donate blood as they develop comorbidities and infirm health. The increase in demand for blood combined with a declining supply line for blood products is expected to result in a severe shortage of blood products in the foreseeable future [18]. Since the development of an effective, safe, hemoglobin-based oxygen carrier (i.e. blood substitute) has been extremely slow, there is little hope that one will be approved in the near future. The weight of evidence argues that blood conservation and transfusion avoidance can benefit individuals as well as the health care system and society as a whole. This effort has important implications for patients at high risk for perioperative transfusion and high blood loss surgical procedures performed on pediatric patients.

Surgical Procedures and Patient Variables: Risk of Perioperative Transfusion

The Pediatric Perioperative Cardiac Arrest Registry [19] and the Mayo Clinic [20] have reported that inadequate fluid and blood administration as well as electrolyte derangements secondary to massive transfusion account for a significant proportion of perioperative cardiac arrests and deaths in children. In order to formulate individual anesthetic plans, anesthesiologists attempt to identify high risk scenarios that result from the proposed surgical procedure and/or the patient's risk factors for massive bleeding. A list of these high-risk-of-bleeding procedures is presented in Table 7.1. Numerous techniques have been developed to avoid or reduce allogeneic blood transfusion (ABT) in procedures such as cardiac surgery, craniofacial reconstruction, and posterior spinal fusion.

When estimating the potential for intraoperative transfusion, one must also consider patient risk factors. Congenital coagulopathies may go undetected for years, only to be uncovered by preoperative testing [21] while coagulation defects associated with NSAID and anticoagulant therapy are readily identified. Severe sepsis or shock of any etiology are commonly associated with disseminated intravascular coagulation (DIC) and should prompt the appropriate preoperative laboratory investigation. A distinct form of coagulopathy that is triggered by hypoperfusion and worsened by hypothermia [22] occurs early in the course of severe trauma and hemorrhagic shock. The rapid treatment of this condition may not only improve postoperative outcomes but reduce blood product utilization [23].

As an age group, newborn infants are at the highest risk of receiving an ABT [24, 25]. Several factors account for the increased incidence of transfusion. First, the newborn

Table 7.1 Potential high blood loss procedures in pediatric patients

Head and neck
Craniotomy
Tumors
Vascular malformations
Extensive seizure focus/hemispherectomy
Cranial vault reconstruction/craniosynostosis
Orthognathic procedures
Chest
Cardiac with or without cardiopulmonary bypass
Thoracotomy
Abdomen
Liver transplantation
Hepatic resection
Splenectomy
Wilms tumor
Neuroblastoma
Orthopedic
Scoliosis/spinal deformity
Pelvic-femoral osteotomy
Vascular malformations
Trauma/burns

coagulation system is functionally intact but easily disrupted by critical illness, which results in more blood loss in surgery [26]. Second, in the resuscitation of acute blood loss in the newborn, the combination of a relatively small blood volume and marginal levels of some coagulation factors quickly result in a dilutional coagulopathy which can lead to further blood loss. Third, newborns tolerate hypovolemic anemia very poorly due to an altered Frank-Starling relationship, decreased compliance of the myocardium, and the effects of fetal hemoglobin on oxygen release to tissues.

Perioperative Blood Conservation Strategies

There are currently no consensus guidelines on the transfusion of infants and children. A recent survey of U.S. and Canadian children's hospitals reported a wide variation in their transfusion policies [27]. Even subspecialists in pediatric anesthesiology practicing in the U.K. [28] and France [29] cannot agree on blood conservation measures or transfusion practice. For lack of available evidence, both the American Society of Anesthesiologists [30] and a collaborative statement from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists [31], specifically excluded pediatric patients from their evidence-based practice guidelines for transfusion. Thus, the inclusion of some information obtained from studies in adults is unavoidable in the any discussion of perioperative blood conservation in children.

Lowering Individual Transfusion Triggers

Lowering the hemoglobin (Hgb) level at which one transfuses RBCs can have a dramatic effect on blood utilization and ABT avoidance [32, 33]. However, lowering the transfusion trigger was not widely accepted until Hebert and colleagues [34], in a multicenter randomized controlled trial (RCT), demonstrated that nonbleeding, critically ill adults tolerated lower Hgb levels without a negative effect on outcome. A study in nonbleeding PICU patients using a similar study design also found no harm in lowering transfusion triggers [35]. Both studies found a substantial reduction in transfusion rates in patients randomized to the more restrictive (Hgb < 7 g/dL) transfusion regimen. Subgroup analyses of the PICU-based study suggested that the lower transfusion trigger regimen had no negative impact on outcomes in children who had undergone cardiac [36] and general surgical [37] procedures. Two similar liberal-versus-restrictive transfusion threshold RCTs in premature infants have provided conflicting results as to the benefit of one transfusion strategy over the other [38, 39].

Institutional Transfusion Guidelines

While lower transfusion triggers should probably not be used as the sole criterion for transfusion, they can be easily incorporated into institutional policies dedicated to avoiding ABT [40, 41]. An institutional program can lower transfusion rates for high blood loss procedures like spinal deformity repair in children [21] and has been recommended for children undergoing craniofacial reconstruction [42]. Compliance surveillance of existing transfusion guidelines in several large neonatal intensive care units was associated with a dramatic decrease in ABTs and blood bank costs without effecting major neonatal outcomes [43]. Intraoperative blood conservation efforts are reinforced by institutional transfusion guidelines that are similarly focused on reducing ABT.

Blood-Sparing Surgical Innovations: Minimally Invasive Craniosynostosis Surgery

Traditional operative methods for cranial vault reconstruction (CVR) require extensive incisions of vascular-rich structures and are associated with the loss of large amounts of blood and the need for nearly universal transfusion [44]. A recent review of blood management for CVR using traditional surgical techniques reported a 100 % transfusion rate with a mean volume of intraoperative transfused RBCs of 51 ml · kg^{-1} [45]. In light of this information, one of the more impressive achievements in the realm of blood conservation in pediatric surgery has been the development of minimally

invasive approaches to cranial vault reconstruction (CVR) for the treatment of craniosynostosis [46]. Endoscopic strip craniectomy (ESC) with postoperative helmet modeling [47] and spring mediated cranioplasty (SMC) [48] are the most widely accepted minimally invasive CVR techniques focusing on ABT avoidance. An early description of ESC reported significantly less bleeding and need for transfusion than traditional approaches [49]. This has been confirmed by two independent groups of investigators [50, 51] who found that between 6 and 8 % of ESC patients required ABT in the perioperative period. The vast majority did not require postoperative PICU admission and were discharged home on the first postoperative day. Two retrospective studies published in 2003 compared SMC to traditional craniosynostosis surgery and found significantly less blood loss and need for ABT in the SMC group [52, 53]. One center's subsequent experience with 100 patients undergoing SMC noted that none of the children needed either transfusion or PICU admission [54]. Both ESC and SMC appear to lower transfusion and PICU admission rates, shorten length of stay, and reduce costs, making these techniques attractive alternatives to traditional CVR in patients diagnosed early in infancy with craniosynostosis.

Antifibrinolytic Agents

The ability of certain compounds to inhibit the fibrinolytic system, thereby reducing blood loss during surgery has come under considerable scrutiny in the past decade. The complex human coagulation system is normally balanced between clot formation and fibrinolysis. Extensive tissue injury associated with surgery or trauma preferentially activates the fibrinolytic pathway with the conversion of inactive plasminogen to plasmin which then cleaves fibrin, leading to clot lysis and further bleeding and coagulopathy [55]. Three inhibitors of fibrinolysis have been used clinically to reduce blood loss and transfusion requirements in surgery: aprotinin (APR), epsilon-Aminocaproic Acid (EACA) and tranexamic acid (TXA). APR was removed from the market in 2008 based on mortality data from the BART study [56] which compared it with EACA and TXA in high-risk cardiac surgery patients. Because APR is no longer available and two meta-analyses [57, 58] and a qualitative review [59] of studies in pediatric surgical patients have found these three drugs to be equally efficacious in reducing surgical blood loss, APR will not be specifically discussed. A similar comparison of adult studies revealed near equivalence of the three agents in avoiding perioperative ABT [60].

Epsilon Aminocaproic Acid (EACA)

EACA, like TXA, blocks binding of plasminogen to fibrin, thereby preventing the activation of plasmin. The clinical use of EACA in both adults and children has largely been limited to cardiac and orthopedic procedures where pathologic fibrinolysis would be expected to result in bleeding. There have been no RCTs of EACA in children published since the meta-analyses of Tzortzopoulou [57] and Schouten [58]. However, the sudden loss of availability of APR and subsequent substitution of EACA and TXA has allowed for several retrospective, comparative studies in infants and children undergoing cardiac surgery at a single center in Germany [61–64]. The results of these studies support the notion that, in terms of their blood sparing effect, EACA and TXA are perhaps slightly less efficacious than APR and equivalent to each other.

Tranexamic Acid (TXA)

A multicenter RCT involving over 20,000 adult trauma patients has recently increased interest in TXA as an antifibrinolytic agent and resuscitation adjunct [65]. When administered to patients who were at risk for, or actively, bleeding, TXA reduced all-cause mortality as well as death from bleeding, without effecting the rate of ABT. Two RCTs have extended the use of TXA in children beyond cardiac and major spinal surgery and into craniofacial reconstruction [66, 67]. Despite some methodological differences, including different dosing regimens, both studies found that, compared with placebo, TXA reduced the need for ABT in these high blood loss procedures.

In numerous reports on pediatric [57, 58] and adult patients [60] [65] the safety profile of TXA has never been questioned. However, two retrospective studies in children comparing TXA to APR [61] and EACA [62] found an increased incidence of seizures in the TXA groups, however, this difference was not statistically significant. Larger retrospective studies in adults undergoing cardiac surgery have been more definitive, showing a statistically significant increase in the postoperative incidence seizures with TXA compared with EACA [68, 69]. It is unknown why cardiac surgery patients may have an increased risk of seizures when given TXA but higher doses and concomitant use of Factor VIIa may play a role [69]. High doses of TXA ($\geq$100 mg $\cdot$ kg^{-1}) in children undergoing cardiac surgery should be used cautiously pending the results of large scale RCTs designed to answer this question.

Preoperative Autologous Donation

There are no randomized, controlled trials in children comparing preoperative autologous donation (PAD) alone with standard management techniques during high blood loss procedures. Most reports have been retrospective case series or cohort studies and many have combined PAD with other blood conservation measures, making the evidence in favor of PAD difficult to assess. The obvious advantage of PAD is

avoidance of ABT and its attendant risks, including life-long alloimmunization [70]. However, the list of problems associated with PAD in pediatric patients must be considered when planning for autologous blood. These include the increased cost of PAD and mandatory wastage of unused PAD units (30–50 % of donated units), the logistics of repeated blood collection (especially in younger children), and the unavoidable risks of bacterial contamination, wrong-unit-transfused errors and effects of the storage lesion. To complicate matters further, three separate meta-analyses [71–73] have shown that, although PAD reduces ABT, it increases the overall incidence of transfusion (autologous and/or allogeneic) which increases patients' exposure to these same risks of transfusion and mistransfusion. These concerns, coupled with the decreasing infectious risks of banked blood, have led to a decrease in PAD use [74] and a call for more convincing evidence of how and when it should be used [75, 76]. There is no disagreement among experts that the same criteria for prescribing an allogeneic blood transfusion should be applied to PAD blood.

Scoliosis surgery in healthy adolescents and cardiac surgery have been studied most extensively in regard to the use of PAD. These procedures are predictably associated with large amounts of blood loss and can be planned for in advance with several preoperative donation sessions [70, 77] In case series in which PAD was the sole blood conservation method, the avoidance of allogeneic transfusion was achieved in 73-89 % of subjects undergoing scoliosis surgery [78–80]. PAD was the sole conservation measure used for younger children undergoing cardiac surgery in several case series from Japan which had ABT avoidance rates greater than 95 % [81–83]. Many of these young children required repeated deep sedation or general anesthesia to facilitate blood donations as reported in infants being prepared for craniofacial reconstruction [84]. The increased cost in material and human resources and the added risk of the multiple anesthetics required for PAD in younger children make this technique less desirable than other modalities.

Cell Salvage Techniques

Intraoperative cell salvage (ICS) involves the recycling of shed RBCs by a collection, purification and concentration process that allows for safe autotransfusion of the product [85]. This technique, used in major non-cardiac and cardiac surgery in adult patients, has been shown to be an effective blood conservation method in numerous RCTs. A meta-analysis of 75 studies in which ICS was the sole conservation modality found an absolute reduction risk of ABT of 21 % [86]. Such high quality studies are lacking in the pediatric population and practitioners must rely on case series, uncontrolled trials or retrospective evidence to guide them.

Early reports of ICS in children suggested that only larger patients with larger shed blood volumes benefited from this technique [87]. However, the advent of cell salvage devices equipped with small volume collecting bowls allowed for more rapid processing and transfusion of smaller volumes of shed blood with avoidance of ABT in smaller patients [88]. Studies using pediatric bowls in infants and young children undergoing craniosynostosis [89, 90], cardiac [91] and orthopedic [92] procedures have reported significant reductions in ABT when ICS was compared with historic or non-randomized controls.

The transfusion of unwashed shed blood in the postoperative period in adult patients appears to have some efficacy in ABT reduction but has been plagued by safety concerns due to high levels of inflammatory mediators, fat particles, activated leukocytes and platelets, and other contaminants in the product [93]. Others have questioned the utility of using shed blood given the relatively small volumes that can be collected (approximately the equivalent of one blood unit in adult patients) and the product's low hematocrit (usually around 30 %) [94]. Pediatric applications of this technique have been developed [95, 96] but there is still a paucity of evidence to recommend it at this time.

Deliberate Hypotension

The use of anesthetic and/or vasoactive agents to deliberately induce hypotension and, thereby, reduce blood loss has been an accepted methodology in anesthesia for many years. Deliberate hypotension (DH) has been studied in adults undergoing major orthopedic and orthognathic procedures and found to be an effective method for ABT avoidance [97]. When DH is used as the sole blood conservation modality for healthy individuals it has been shown to have minimal impacts on vital organ perfusion and serious complications are rare [98].

There is little high level evidence showing that DH as a sole modality reduces ABT rates in pediatric patients but, based on adult studies, DH is routinely used in adolescents undergoing scoliosis surgery. A single-blind study in adolescent patients undergoing orthognathic surgery reported less blood loss in the DH group compared to controls, but the blood loss was so small that no subject in either group required transfusion [99]. The only randomized, controlled trial of DH in infants reported a significant reduction in blood loss in the hypotensive group during craniosynostosis surgery [100]. DH is frequently used with acute normovolemic hemodilution (ANH), PAD, ICS, or a combination of these and other blood sparing techniques. The combination of DH with extreme normovolemic anemia has been reported in pediatric patients [101, 102]. However, this approach should be undertaken with caution because it may result in inadequate oxygen delivery to vital organs [103].

Acute Normovolemic and Hypervolemic Hemodilution

Acute Normovolemic Hemodilution (ANH) is performed after the induction of anesthesia and prior to surgical incision by removing blood from the patient and replacing it with crystalloid and/or colloid solutions to lower the hematocrit while maintaining normovolemia [104]. When surgical bleeding commences, it occurs at a lower Hct and is replaced with more crystalloid until the targeted nadir Hct is reached. The harvested blood is kept in the operating room and returned to the patient when either ongoing blood loss requires transfusion or the blood loss has ceased. This technique preserves platelet and clotting factor functions and eliminates bacterial contamination, clerical error and storage lesion concerns associated with banked blood. The question as to the efficacy of ANH in reducing ABT has been addressed by investigators over the years with no clear answer due to conflicting results, study heterogeneity, design flaws, and lack of blinding [73, 105, 106]. Large, well designed RCTs are needed to address these concerns and to establish ANH's role in perioperative blood management.

Healthy children and adolescents have excellent physiologic reserve and tolerate even extreme ANH quite well. Studies targeting nadir hematocrits as low as 9 % in adolescents [107] and 17 % in children 1–8 years old [108] found that delivery-dependent oxygen consumption was not reached before the subjects' blood was re-infused. ANH has been successfully used as the sole blood sparing modality in children undergoing bone marrow harvest [109], craniosynostosis [108, 110] and scoliosis surgery [111, 112] but there have been no RCTs in pediatric patients.

It should be remembered that young infants may not tolerate ANH. In response to ANH an increase in cardiac output occurs that is due, in part, to an increase in stroke volume. Additionally, the oxygen extraction ratio increases and oxygen consumption is maintained [113]. Infants less than 4–6 months of age cannot increase stroke volume to the extent that older individuals can. This same age group has varying amounts of Hgb F still in circulation which does not release oxygen to tissues as well as Hbg A. Thus, they may not be able to increase oxygen extraction to help compensate for ANH reductions in oxygen delivery. Another group of pediatric patients that does not appear to tolerate hemodilution are infants and children having open heart surgery. Regional cerebral oxygenation was shown to be significantly decreased in hemodiluted (intraoperative Hct fo 16 %) children during cardiac surgery [114]. In a RCT of infants undergoing cardiac surgery, moderate hemodilution (intraoperative Hct of 21.5 %) was associated with poorer performance on tests of psychomotor development at 1 year of age. Long term follow up of these children is needed to determine whether these developmental delays are persistent.

Hypervolemic Hemodilution (HH) offers a simpler alternative to ANH for anticipated blood losses of less than 40 % of the patient's blood volume [115]. HH involves the preoperative infusion of colloid equivalent to approximately 20 % of the patient's blood volume followed by maintenance of this hypervolemic state with crystalloid throughout surgery. When HH was compared with ANH in two RCTs in adults having moderate blood loss procedures, the two were found comparable with regard to ABT avoidance [116, 117]. The only RCT in children comparing HH to standard practice found that HH did not eliminate ABT but did significantly reduce the volume of transfused RBCs [118]. This technique will likely be utilized more in pediatric patients in the future.

Preoperative Erythropoietin Administration

The preoperative use of human recombinant erythropoietin (EPO) to increase red blood cell mass as part of a blood conservation program began shortly after its release in 1988 [119]. In subsequent years EPO's role in perioperative blood management became more well defined but cost concerns limited it's use for this purpose in the U.S. [120]. Early reports in pediatric patients demonstrated the blood sparing potential of EPO in neurosurgical [121], craniofacial [122], and spinal surgery [123] cases. A randomized, controlled trial of preoperative EPO administration for cranial vault remodeling demonstrated a reduction in the ABT rate in children given EPO (57 %) compared with controls (93 %). However, this study and others cited above indicate that EPO therapy alone cannot eliminate the need for transfusion in all children and should be used selectively or in combination with other blood sparing modalities.

Following adult studies which demonstrated efficacy, EPO was added to a number of pediatric PAD regimens in order to facilitate autologous donation prior to cardiac [124, 125], scoliosis [126], and craniofacial [124] surgery. EPO improved compliance rates for donation and left patients with a higher Hct on the day of surgery, compared to patients who underwent PAD alone, which contributed to reduced perioperative ABT [125, 126]. For infants having craniofacial reconstruction, preoperative EPO therapy plus intraoperative cell salvage resulted in significant ABT avoidance compared to controls who received standard perioperative blood management [127]. EPO has also been used to increase preoperative red cell mass and improve the efficacy of ANH [128, 129] in craniofacial reconstructive surgery. These studies support the use of EPO as an adjunct to other blood

conservation measures and points the way to a multimodal approach to perioperative blood management.

Multimodal Blood Conservation

The combined use of several blood conservation techniques to completely eliminate ABT in patients of the Jehovah's Witness faith have demonstrated the feasibility and effectiveness of "bloodless surgery" in patients of all ages [130–134]. Lisander and colleagues [135] have demonstrated that a multimodal approach was more efficacious than using a single modality which did no better than the control group in avoiding ABT. A multimodal approach usually incorporates a conservative (low) transfusion trigger and the use of a hospital or specialty-wide transfusion algorithm along with some form of autologous blood collection (PAD, ANH, ICS), DH when appropriate, and, possibly, EPO therapy. A policy of conservative postoperative blood sampling may also reduce phlebotomy blood loss which can result in the development of anemia and the need for ABT [136]. Blood conservation modalities can be combined in a variety of ways but one caveat of the intraoperative management is that oxygen delivery should not be reduced below that needed to maintain delivery-independent oxygen consumption (critical oxygen delivery). Inadequate oxygen delivery is possible when DH and ANH are combined to excess (blood pressure to low, Hgb too low) or used in the wrong patient.

Many institutional blood conservation programs have adopted multimodal protocols that can be safely applied to the individual patient to achieve significant reductions in ABT [21, 84, 137–141]. Perioperative blood conservation requires that physicians, nurses, blood bank and laboratory personnel adhere to the care plan over the duration of the patient's hospitalization. Some of the long term benefits that accrue from reducing ABTs are slowly becoming apparent. Currently, these are overshadowed by the many known transfusion-related complications that can be avoided with an effective blood conservation program for pediatric patients.

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Malignant Hyperthermia

8

Thierry Girard and Albert Urwyler

Abstract

Malignant hyperthermia (MH) is an uncommon, life-threatening pharmacogenetic disease, triggered by halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Pediatric intensive care specialists may be confronted with MH in various circumstances: (i) intensive care treatment of a patient presenting with an acute episode of MH, (ii) intensive care treatment of a patient with known MH susceptibility or a suspected history for MH susceptibility, (iii) differential diagnosis of patients presenting with hypermetabolic disorders and/or rhabdomyolysis. Although the triggering mechanisms of MH are not yet fully elucidated, it is well known, that various single point mutations in genes involved in excitation-contraction (EC) coupling of skeletal muscle are causative for MH susceptibility. The most important genetic locus is the RYR1 gene encoding the protein for the calcium channel of the sarcoplasmic reticulum. If MH susceptible individuals are given volatile anesthetics and/or succinylcholine, MH may be triggered. These triggering agents may cause a loss of intracellular calcium control in skeletal muscle, leading to skeletal muscle hypermetabolism, causing metabolic and respiratory acidosis and various consecutive life threatening symptoms if treatment is not initiated immediately. Corner stones of a successful therapy are (i) immediate cessation of triggering agents, (ii) application of dantrolene and (iii) symptomatic treatment of additional clinical and laboratory findings seen during an MH episode. After any clinical MH episode the patient, and in case of a positive finding his or her relatives, must undergo a systematic MH diagnostic workup. Individuals and family members with MH susceptibility should get appropriate information and a warning card for MH. It may be postulated that any loss of myoplasmic calcium control is causing hypermetabolism in various diseases different from MH (e.g. exercise hypermetabolism, heat stroke, sepsis) and thus, similar therapeutic approaches to MH treatment may be applied.

Keywords

Malignant hyperthermia • Dantrolene • Pharmacogenetics • Skeletal muscle • Volatile anesthetics

Malignant hyperthermia (MH) is an uncommon, life-threatening pharmacogenetic disease, triggered by halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine. The first description of MH was published 1960 by Denborough and Lovell, which suggested MH to be an inherited disorder [1]. Indeed, subsequent investigation of the family tree by these same authors showed a dominantly inherited genetic disorder published in a second paper with the full description of the case and the family history [2]. The observation that freshly biopsied muscle strips from patients having survived MH were more sensitive

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to caffeine and halothane in vitro compared to muscle strips from individuals with no history of MH, allowed the development of diagnostic protocols for the investigation of MH susceptibility [3–5]. Screening of suspected MH susceptible individuals and their family members led to the identification of MH causative genetic mutations and non-invasive genetic screening of families with identified MH mutations.

In 1990, the genetic locus for MH susceptibility was identified on human chromosome 19 (RYR1-gene encoding the ryanodine receptor protein or calcium channel of the sarcoplasmic reticulum in skeletal muscle) [6, 7]. However, several researchers demonstrated heterogeneity of MH susceptibility [8]. Thus, it became clear that MH is not a monogenic disorder, even if one single point mutation in many families may be identified and then be used for the non-invasive diagnosis in these MH families [9, 10]. Evidence for alternative genetic loci in addition to RYR1 in humans was demonstrated on chromosomes 3, 7 and 17, whereas causative mutations were localized in the alpha 1-subunit of the human dihydropyridine-sensitive L-type calcium-channel receptor in skeletal muscle on chromosome 7q [11–13]. An actual list of causative mutations for MH is available on the website of the European Malignant Hyperthermia Group [14].

The pathophysiology of MH is explained by the loss of myoplasmic calcium control in skeletal muscle of MH susceptible individuals. Trigger agents (all halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine) may increase the myoplasmic calcium concentration in MH susceptible individuals causing an increase of skeletal muscle metabolism [15]. MH may be life threatening if not immediately diagnosed and correctly treated. The most important components of a successful treatment include [16] early diagnosis (unexplained increase of endtidal CO_2, metabolic acidosis), immediate cessation of trigger agents, and dantrolene treatment (Fig. 8.1).

Pediatric intensive care specialists may be confronted with MH in various circumstances. For example, pediatric intensive care specialists may be called upon to provide intensive care treatment of a patient presenting with an acute episode of MH, e.g. after MH is diagnosed during or after induction of anesthesia using trigger agents. Anesthesiologists should alert the intensive care team and be available for assistance with ongoing treatment in the ICU. Tables 8.1, 8.2, and 8.3 present detailed information on the early and late clinical symptoms of MH, differential diagnosis, and concepts for appropriate treatment [16]. Modern digital electronic devices, such as iPhone or iPad applications are now available, which may be helpful for a systematic approach [17, 18]. Following a suspected MH episode, the patient should be referred to a MH diagnostic center for a diagnostic workup. A list of centers in Europe is presented on the website of the European Malignant Hyperthermia Group (www.emhg.org). Similarly, a list of centers in the United States is presented on the website of the Malignant Hyperthermia Association of the United States (www.mhaus.org). The patient and his family should get appropriate genetic counseling and a warning card about MH.

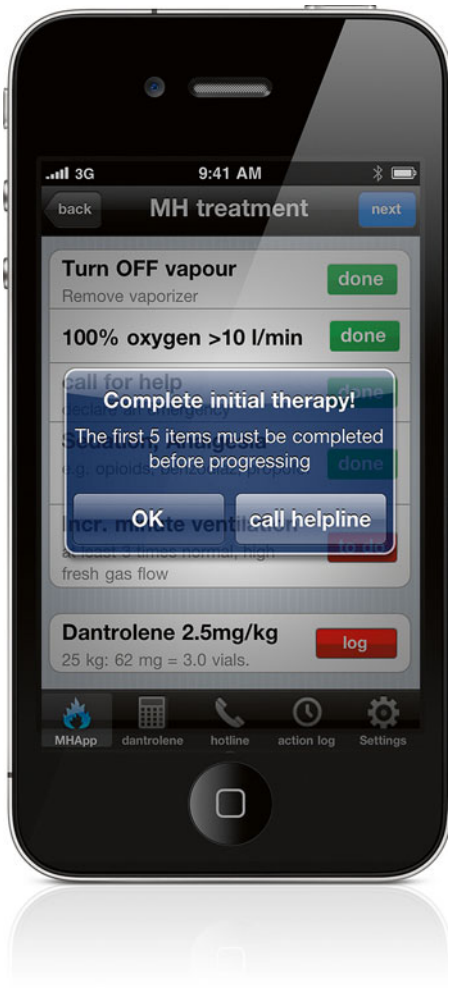

Fig. 8.1 Treatement screen of iPhone application MHApp. This application might be used for training, teaching and treatment of MH episodes

Alternatively, if a patient with known or suspected MH susceptibility is treated for any reason in the ICU, trigger agents (all volatile anesthetics and succinylcholine) must be strictly avoided. Whether some patients without MH susceptibility may develop an MH-like hypermetabolic syndrome has not been systematically proved. However, it may be speculated, that a genetic predisposition with minor degree of abnormal myoplasmic calcium regulation may develop an MH-like syndrome, which may be treated according to effective MH therapy. Selected myopathies, i.e. central core disease (CCD), multi minicore disease (mMD), nemaline myopathy and King-Denborough myopathies are associated

Table 8.1 Clinical signs of MH

Early signs
Metabolic
Inappropriately elevated CO_2 production (raised end-tidal CO_2 on capnography, tachypnea if breathing spontaneously)
Increased O_2 consumption
Mixed metabolic and respiratory acidosis
Profuse sweating
Mottling of skin
Cardiovascular
Inappropriate tachycardia
Cardiac arrhythmias (especially ectopic ventricular beats and ventricular bigeminy)
Unstable arterial pressure
Muscle
Masseter spasm if succinylcholine has been used
Generalized muscle rigidity
Later signs
Hyperkalemia
Rapid increase in core body temperature
Grossly elevated blood creatine phosphokinase levels
Grossly elevated blood myoglobin levels
Dark-colored urine due to myoglobinuria
Severe cardiac arrhythmias and cardiac arrest
Disseminated intravascular coagulation

Adapted from Glahn et al. [16]. With permission from Oxford University Press

Table 8.2 Differential diagnosis of MH

Inappropriate anesthesia, analgesia, or both
Infection or septicemia
Insufficient ventilation or fresh gas flow
Anesthetic machine malfunction
Anaphylactic reaction
Pheochromocytoma
Thyroid crisis
Cerebral ischemia
Neuromuscular disorders
Elevated end-tidal CO_2 due to laparoscopic surgery
Ecstasy or other dangerous recreational drugs
Malignant neuroleptic syndrome

Adapted from Glahn et al. [16]. With permission from Oxford University Press

with malignant hyperthermia [19]. Triggering agents must be avoided in these patients. Other myopathies, such as muscular dystrophies and mitochondrial myopathy seem not to be associated with MH [19], although succinylcholine should be avoided in all myopathic patients.

Finally, there are several disorders mimicking MH-like symptoms (see Table 8.2). The differential diagnosis can be quite challenging. With the exception of a fulminant MH episode, diagnosis of MH is frequently difficult. Treatment with dantrolene should be initiated even if there is no clear

Table 8.3 MH Treatment

Stop all trigger agents immediately
Hyperventilate (use a minute volume 2–3 times normal) with 100 % O_2 at high flow
Declare an emergency and call for help
Change to non-trigger anesthesia (TIVA)
Inform the surgeon and ask for termination/postponement of surgery
Disconnect the vaporizer—do not waste time changing the circuit/anesthetic machine
Dantrolene
Give dantrolene 2–2.5 mg/kg i.v. (ampoules of 20 mg are mixed with 60 ml sterile water)
Obtain dantrolene from other sources, for example, pharmacy/nearby hospitals—at least 36–50 ampoules may be needed for an adult patient
Dantrolene infusions should be repeated until the cardiac and respiratory systems stabilize
The maximum dose (10 mg/kg) may need to be exceeded.
Monitoring
Continue routine anesthetic monitoring (SaO_2, ECG: Electrocardiogram, NIAP: Non invasive arterial pressure, ETCO2: End-tidal CO2)
Measure core temperature
Establish good i.v. lines with wide-bore cannulas
Consider inserting an arterial and central venous line, and a urinary catheter
Obtain samples for measurement of K+, CK, arterial blood gases, myoglobin, and glucose
Check renal and hepatic function and coagulation
Check for signs of compartment syndrome
Monitor the patient for a minimum of 24 h (ICU: Intensive care unit, HDU: high-dependency unit, or in a recovery unit)
Symptomatic treatment
Treat hyperthermia
Chilled 0.9 % saline i.v.
Surface cooling: wet, cold sheets, fans, and ice packs placed in the axillae and groin
Other cooling devices if available
Treat hyperkalemia
Dextrose/insulin
Dialysis may be required
Treat acidosis
Hyperventilate to normocapnea
Give sodium bicarbonate i.v. if pH <7.2
Treat arrhythmias
Amiodarone
Beta-blockers (e.g. propranolol/metoprolol/esmolol)—if tachycardia persists
Maintain urinary output >2 ml/kg/h
Furosemide 0.5–1 mg/kg
Mannitol 1 g/kg

Adapted from Glahn et al. [16]. With permission from Oxford University Press

Consult your local Malignant Hyperthermia Investigation Unit about the case

Patients suspected of being MH-susceptible should undergo diagnostic testing using in vitro contracture testing (IVCT) at a designated MH-laboratory (United States: www.mhaus.org; Europe: www.emhg.org)

MH diagnosis, as delayed treatment can be deleterious. Due to the mode of action dantrolene can lead to muscle weakness. The drug is hyperosmotic and can provoke phlebitis.

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Part II

General Principles of Peri-operative Care

Michael R. Anderson

Peri-operative Care of the General Pediatric Surgical Patient

9

Robert T. Russell, David E. Carney,
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Abstract

Perioperative management of newborn and infants is quite different from the perioperative management strategy in adults. Infants have quite a different response to surgical disease and intervention that must be recognized by the clinician. Thermoregulation, metabolic changes, resuscitation principles, fluid and electrolyte management, and nutritional needs are quite different in the pediatric population. Not only are physiologic parameters different, but also many of the pediatric surgical anomalies and surgical diseases are unique. This chapter will discuss critical details of perioperative management of neonates and infants and highlight specifics that are unique to various common surgical anomalies.

Keywords

Pediatric surgery • Fluid resuscitation • Preoperative preparation • Intestinal obstruction

Introduction

In many ways, the physiologic response to surgical stress in children and adolescents mimics that of adults. However, newborn and older infants have a different response to surgical disease and intervention, particularly with respect to thermoregulation, metabolic function, and fluid and electrolyte balance. This chapter will discuss basic physiologic changes following surgical procedures in neonates and infants, emphasizing important principles of resuscitation. This chapter will also highlight common pediatric surgical anomalies and discuss specific details that are critical to the perioperative management of infants with specific congenital lesions.

Thermoregulation in the Pediatric Surgical Patient

The instinctive desire of the newborn is to maintain core temperature while limiting metabolic demand. This equilibrium is maintained by a delicate balance between heat production and heat loss. Mechanisms to produce heat include voluntary muscle activity and involuntary muscle activity. Involuntary activity includes both shivering and non-shivering (metabolizing brown fat). Specifically, in response to a cool environment, healthy infants will cry and move to generate heat or assume the fetal position to limit exposed surface area in order to reduce loss of heat. Obviously these methods are

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compromised in the ill or sedated infant. In addition, anesthesia may interfere with non-shivering thermogenesis [1]. The next line of defense is peripheral vasoconstriction and central shunting. When these methods cannot maintain core temperature, non-shivering thermogenesis begins. Complex signal transduction begins with temperature sensors in the skin that transmit a message to the hypothalamic ventromedial nucleus ultimately leading to norepinephrine stimulation of receptors in the brown fat. Finally, oxidation of glycerol and fatty acids produces heat [2]. The hypothermic neonate can develop neonatal cold injury syndrome manifesting as lassitude, respiratory depression, apnea, bradycardia, metabolic acidosis, hypoglycemia, hyperkalemia, and oliguria [3]. If not prevented, this avoidable problem will only complicate the post-operative management.

Perioperative hypothermia may not only increase the risk of wound infections [4], but the symptoms of hypothermia create unnecessary concern that results in excessive interventions to eliminate the possibility of a postoperative complication, specifically sepsis. The mechanisms of heat loss by convection, conduction, and evaporation are often exaggerated in the postoperative period by open wounds and fluid losses from surgical drains and tubes. Common practices to maintain temperature control include the use of humidified and heated inhalant gases, warmed fluids, and increasing the ambient temperature of the operating room to limit heat loss during anesthesia. Placing a hat on the newborn will limit evaporative heat loss because of the relatively large percentage of total body surface area of the head in the newborn. Similarly, using soft wraps on the extremities during the operation will limit evaporative heat loss. Skin preparation solutions and any fluids used for irrigation should also be warmed. Postoperatively, once in the intensive care unit (ICU), most post-surgical infants are best managed on a radiant warmer with skin thermistor-activated servo-control mechanism [5]. Importantly, warmers simultaneously maintain precise thermoregulation and provide unparalleled visibility of the infant. Since serial exams of the thorax and abdomen are common for most surgical patients, a radiant warmer avoids heat loss associated with repeated unbundling of infants not housed in warmers. Additionally, the ease in which the infant may be accessed avoids bundling and reduces the likelihood of inadvertent and premature removal of necessary lines, tubes and drains.

Metabolic Changes from Surgical Stress

In all children, the neuroendocrine response to surgical stress alters metabolism, resulting in a catabolic state. The body's energy reserves are mobilized in response to surgical stress. Following surgical intervention, increased levels of glucocorticoids, catecholamines, and endorphins are the principle initiators of this defense mechanism to mobilize stored energy reserves. Anesthetic agents, particularly halothane and fentanyl, can suppress this metabolic response to stress [6]. Other perioperative factors which may prolong or intensify this catabolic response include the condition of the infant prior to operation (i.e. the presence of peritonitis), the type, extent, or duration of the surgical procedure, associated blood loss, and the inherent condition of the neonate (i.e. prematurity, hypothermia). This is often detrimental because newborns and sick infants are inherently at risk for prolonged catabolism and frank hypoglycemia due to immature gluconeogenesis and poor glycogen stores. These limitations are only compounded by the high metabolic demands imposed by growth, maturation, and adaptation after birth.

Following routine surgical procedures, the infant's energy expenditure does not increase substantially if there has not been a period of starvation prior to surgical intervention. In the early postoperative period following either non-routine or stressful interventions, the infant is in a state of catabolism. In both scenarios excessive supplemental nutrition in the early postoperative period can be detrimental. Specifically, neonates may demonstrate increased *de novo* lipogenesis [7]. Any additional carbohydrates administered in the face of adequate glycogen stores are shuttled into the lipogenic pathway. This may lead to fatty infiltration of the liver and increased carbon dioxide production which can be problematic for preterm infants or newborns with respiratory insufficiency, such as those requiring mechanical ventilation. Early postoperative parenteral nutrition can result in significant rate of weight gain from both solid tissue and water accumulation.

These concerns raise the obvious question of how to replete nutrition during this period of extreme catabolism. In the early postoperative period overfeeding may be avoided by administering adequate protein (2.0–2.5 g/kg/day) while limiting total calories (including protein) to maintenance levels. In general, supplementation in the postoperative period begins with 10 % dextrose, 2.0 g/kg/day protein and 1.0 g/kg/day lipids. This initially provides almost 60–75 kcal/kg/day. Once the child is no longer catabolic one can gradually increase the concentration based on serum glycemic control, presence of glucose in the urine, and serum triglyceride levels. Although significant data specifically for children does not exist, controlling hyperglycemia dramatically reduces mortality in adults [8, 9]. Newborn infants require 100–200 kcal/kg/day for normal growth. This is increased during stress, cold, infection, surgery, and trauma. A valuable method that estimates target caloric requirements is to recognize that for a well infant 17.5 % dextrose, 3.0 g/kg/day of protein and 3.0–4.0 g/kg/day of fat at a rate determined by maintenance fluid requirements will provide 110–120 kcal/kg/day. Postoperative nutritional support may be made

more efficient by initially titrating up to this composition and subsequently tailoring the formula based on individual patient needs, including appropriate weight gain of 15–30 g/day once euvolemia is restored. In any post surgical patient oral hydration and oral feeding are optimal if the gastrointestinal tract is functional.

Metabolism of hemoglobin is well described elsewhere in this text however it requires brief mention here. Following surgery a reprioritization of acute phase protein production occurs. Similar to the immature liver of preterm infants, the ability of the liver to conjugate bilirubin is reduced following stressful surgery. As a result of this relative hepatic insufficiency, *physiologic* jaundice may be more pronounced and of longer duration in newborns who undergo early operative intervention. Management by accepted AAP guidelines is optimal [10].

Fluid and Electrolyte Balance Following Surgery

Prior to considering how to resuscitate the post-surgical infant or child, we must first consider how surgical stress affects renal function following surgery. A low glomerular filtration rate and limited ability to concentrate urine makes infants less tolerant of dehydration. Furthermore, the increased metabolic activity of the neonate increases the production of solute to be excreted in the urine. Therefore, newborn infants often require 2–4 mL/kg/h urine production to clear the renal solute load. This may be difficult in the neonate who has recently undergone a major operation.

When considering how to resuscitate any patient, one must first recognize the deficits requiring replacement. Water represents 70 or 80 % of the body weight of the normal neonate and premature baby, respectively. This percentage decreases with age and ultimately matches that of the adult in the post-pubescent adolescent. The percentage of total body water increases with lean body mass and varies inversely with fat content (preterm infants have less subcutaneous fat). Due to their increased surface area, heat loss is a more significant factor in infants than adults. The two major sites for insensible water losses are from the lung (~1/3) and skin (~2/3). Fecal losses are negligible for purposes of estimating maintenance fluid needs. Also, insensible water loss is affected by gestational age, body temperature (radiant warmers), and phototherapy. Prematurity, warmers, fever, wounds and assisted ventilation are all part of postsurgical care, yet their presence can complicate the determination of maintenance fluid needs. Since most of these factors are practically unquantifiable, the fundamental basis upon which both insensible water loss and urine loss are calculated is caloric expenditure [11, 12].

General Principles of Resuscitation

Significant fluctuations in total body water and extravascular fluid shifts (into both the intracellular and interstitial compartments) can occur in response to acute inflammation following surgery. The degree of postoperative inflammation is related to the extent of the surgery as well as any associated tissue ischemia/reperfusion. Resuscitative efforts should anticipate this postoperative shift. The inflammatory phase typically manifests in the first 12 h after major surgery and may only begin to resolve between the second and third postoperative days. Aggressive resuscitation in neonates and pediatric patients can maintain adequate organ perfusion in the face of accelerating extravascular fluid shifts. This approach should be taken with caution for extremely preterm infants, patients with congenital heart disease, and those with known renal insufficiency. The consequences of excessive fluid administration to preterm infants may include enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage, and reopening or maintaining patency of a patent ductus arteriosus.

Recent concern over the potential dangers of hyponatremia in children receiving hypotonic saline is valid particularly since surgical stress increases antidiuretic hormone levels [13]. However, hypotonic saline solutions can be used safely if administered in a thoughtful manner. In our experience, fluid resuscitation in the postoperative period is typically divided into maintenance and resuscitative fluids. A commonly used maintenance fluid is an iso-osmotic, hypotonic solution such as 10 % dextrose with 0.25 % normal saline. This maintenance fluid may be supplemented with potassium once adequate renal function is restored. This solution, when delivered at appropriate maintenance rates as previously described [11], will replace routine losses of sodium, potassium and water in the urine and insensible losses from sweat, stool, and respiration. In addition to maintenance fluids, resuscitative fluids are administered to replace losses that occur from non-physiologic sources, which include excessive gastrointestinal losses, losses from drains, extravascular fluid shifts, and hemorrhage. Lactated Ringer's is given concurrently to make up for these losses in a volume which matches measured or estimated output. Ideally, the electrolyte composition of the resuscitative fluids is equal to that of the fluids lost. The exact electrolyte composition of body fluids in infants and children is well described and may serve as a guide for fluid replacement, particularly when fluid and electrolyte balance is tenuous. In particular these losses can be optimally replaced in the following manner:

1. Proximal losses (NG suction, vomiting): 0.45 %NS + 20 mEq KCl/L
2. Distal Losses (diarrhea, ostomy, fistulae): Lactated Ringer's solution
3. Third space losses: Lactated Ringer's solution

Once the appropriate resuscitative solution is chosen, then it becomes essential to provide an appropriate fluid challenge. First the physician must have knowledge of the circulating blood volume (neonates 90–100 mL/kg, infants 75–85 mL/kg, older children 70–80 mL/kg, and adults 60–70 mL/kg). This understanding combined with bedside assessment of skin turgor, sunkeness of eyes, moisture content of mucous membranes, presence and quantity of tears, pulse, blood pressure (with pulse pressure noted), urine output, capillary refill time, and neurological status (toddlers and older children) allows for an appropriate fluid bolus to be chosen. This is best highlighted in the example below.

Example 1: A 3.0 kg term infant returns to the intensive care unit following an exploratory laparotomy with limited bowel resection and primary anastomosis for jejunal atresia. Two hours later you are notified that the pulse is 210/min, blood pressure is 58/38 mmHg, capillary refill time is 4 s, and the child has made 2 mL of urine over the previous 2 h. Often this is managed initially with a 10 mL/kg (30 mL) bolus. In fact if we properly assess this infant; the degree of hypotension, oliguria, tachycardia, and malperfusion suggests the neonate is 30 % volume depleted. Accordingly, if the circulating volume is 300 mL (100 mL/kg × 3.0 kg), it follows that nearly 90 mL will be required to obtain a proper initial physiologic response.

Even most children with complex congenital heart disease and renal insufficiency will tolerate initial aggressive resuscitation in this manner. Often it is the acuity with which these children are resuscitated rather than the total amount of resuscitative fluid that becomes overwhelming. In children that respond to aggressive resuscitation with pulmonary compromise, the tendency is to initiate diuretic therapy. However, this practice may be ill-advised in the immediate post-operative period. To eliminate intravascular volume in the acute postoperative period can be hazardous and begin a management plan that oscillates from respiratory distress prompting diuretic therapy to malperfusion leading to fluid boluses. Instead, simply unloading a poorly compliant ventricle with a venodilator will functionally unload the heart while maintaining the circulating blood volume. This management parallels the acute use of nitrates for adults with congestive heart failure. Since more than 60 % of the capacitance of the circulatory system is in the peripheral and central venous system, the liberal use of morphine may be helpful in this regard, which has the dual benefit of venodilation combined with perioperative analgesia. Finally, although information in children is lacking, there is no clear evidence to advocate colloid versus crystalloid fluids in the setting of hypovolemia [14], and many physicians will use crystalloid fluids in this setting, unless blood products are warranted for anemia, thrombocytopenia, or coagulopathy.

General Preoperative Preparation

Preparing an infant or child for surgical intervention requires a thorough history and physical examination. Often attention to the primary anomaly becomes distracting, so a thoughtful secondary survey is critically important, which includes:

1. An evaluation of the prenatal and maternal history and a search for undiagnosed illnesses, disorders or anomalies, specifically genetic syndromes and congenital heart disease.
2. An investigation for unsuspected coagulopathy with the patient, or a family history of bleeding disorders and/or difficulty with anesthesia.
3. An appropriate assessment of the need for blood products. If required, are appropriate quantities available? (Our practice, as well as that of others is to routinely request washed packed red blood cells in all infants and small children since intraoperative and perioperative blood losses often mandate rapid transfusion which can be complicated by lethal hyperkalemia if unwashed cells are used.)
4. An assessment of the presence and ultimate need for intravenous access with consideration of temporary or long-term central venous access.
5. An assessment for antibiotic needs.
6. An assessment of parental awareness of the diagnosis, procedure, anesthetic plan and possible consequences including death.

When preparing for gastrointestinal procedures, most infants can be given clear liquids (including breast milk) up to 4 h prior to operation. Most surgeons would favor Pedialyte over breast milk only if the child has received a bowel preparation. For actual bowel preparation prior to surgery on the gastrointestinal tract, many surgeons provide a mechanical preparation with Golytely 25 mL/kg/h × 4 h, which is best administered through a 5 French nasogastric feeding tube, removed immediately after an adequate result has been obtained. Small infants and children should receive intravenous fluids during and after the preparation. Any patient that has a robust response or has been maintained on parenteral nutrition should have serum electrolytes, including serum magnesium, checked following the mechanical preparation. Utilization of oral antibiotics as part of the bowel preparation has fallen out of favor. A small experience at the J.W. Riley Hospital for Children has not revealed an increase in postoperative wound infections following a mechanical preparation only [15]. Thus we have routinely limited our preparation to mechanical cleansing with Golytely. An exception may be made for infants with short bowel syndrome or other conditions with possible bacterial overgrowth. In contrast, we do maintain the practice of perioperative antibiotics to limit the incidence of wound infections.

Special Considerations with Common Surgical Anomalies

The following discussion will highlight common pediatric surgical lesions, which will include a brief description of the anomaly and its clinical presentation and a limited description of the operative repair. The discussion will focus on preoperative assessment and stabilization followed by strategies for the acute postoperative management, including subtleties to avoid or manage postoperative complications. Importantly, the perioperative management of children with congenital heart disease deserves special attention and is discussed in several chapters elsewhere in this text.

Gastroschisis

Gastroschisis is an anterior abdominal wall defect just lateral to the umbilicus (most often right-sided) resulting in antenatal evisceration of all or part of the peritoneal contents (Fig. 9.1a). The bowel may be foreshortened and matted with an inflammatory exudate due to exposure to the amniotic fluid. Approximately 10–12 % of cases are complicated by intestinal atresia related to segmental volvulus or mesenteric ischemia due to a narrow abdominal wall defect.

The preoperative goals are to appropriately resuscitate the newborn and avoid ongoing fluid and heat losses. Accordingly, our practice, as well as that of many surgeons is to place the infant in a plastic bag (Lahey bag) which encloses the entire infant below the nipples, including all externalized viscera. If unavailable, any clear dressing or plastic wrap is superior to gauze in preventing evaporative losses and does not adhere to the eviscerated intestine. For transport or while awaiting surgical intervention, the infant should be placed in the decubitus position with towels to support the eviscerated mass. This limits the possibility of kinking the mesentery and initiating an ischemic insult. Orogastric decompression is mandatory. Antimicrobial therapy is initiated with

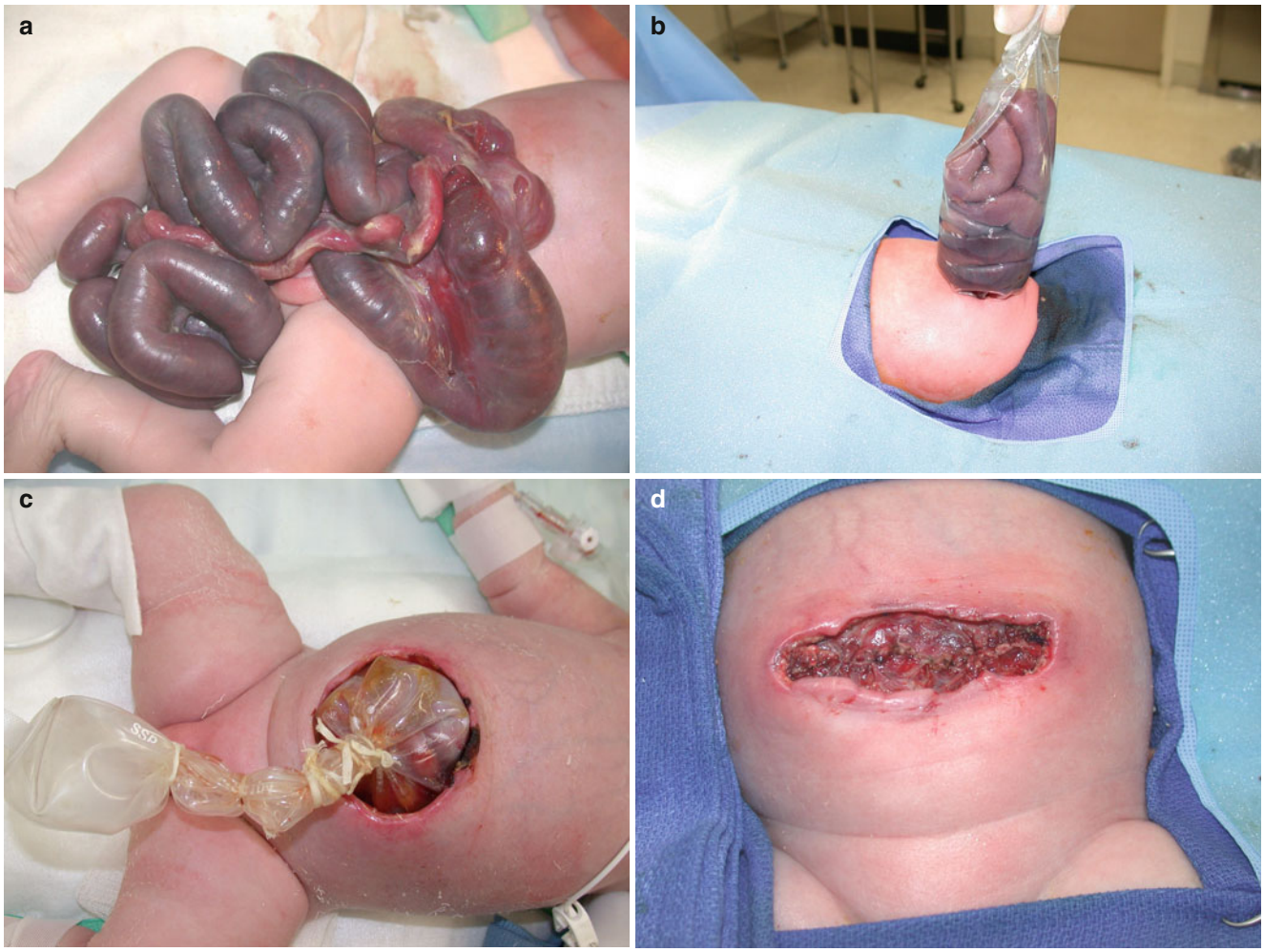

Fig. 9.1 Photo of term newborn infant with Gastroschisis noting the eviscerated intestine at birth (**a**), subsequent bedside placement of viscera into a silastic silo (**b**), the appearance of reduced viscera on day of life five (**c**) and final closure of fascia (**d**)

ampicillin and gentamycin. Once stabilized, the physician should search for associated syndromes and anomalies. Fortunately, gastroschisis has few associated anomalies other than intestinal atresia and undescended testes. If possible intravenous access should be secured in an upper extremity and the infant should be bolused with normal saline in the manner outlined earlier. Once hemodynamically stable, the infant should be immediately transferred to an appropriate referral center where neonatal and pediatric surgical specialists are available.

Almost always, the eviscerated contents include small and large intestine but can include the gonads, stomach, liver, gallbladder, bladder, uterus, and fallopian tubes [16]. There has been near uniform acceptance that initial therapy should include bedside placement of a plastic silo to house the eviscerated contents [17] (Fig. 9.1b). This procedure can be accomplished with intravenous morphine only, almost always avoiding the need for tracheal intubation. Gradual staged reduction of the eviscerated contents housed within the silo is accomplished over the first 5–7 days of life (Fig. 9.1c). Possible surgical outcomes include primary abdominal wall closure if there is complete intestinal continuity, temporary stomas if there is an atresia not amenable to primary anastomosis, or primary closure leaving the atretic bowel in place anticipating a planned second operation around 6 weeks of life to restore intestinal continuity [18, 19]. Fascial repair is accomplished with primary approximation of native fascial tissue or occasionally with the use of fascial substitutes (e.g. Alloderm, SIS) (Fig. 9.1d).

Known acute complications in the post-operative period include acidemia, abdominal compartment syndrome, swollen and/or discolored legs from venous compression, and omphalitis of the anterior abdominal wall. In the early period following placement of the silo it is common for patients to have a mild base deficit. Typically this is not a manifestation of inadequate perfusion and does not require aggressive management, provided the acidemia is not worsening and the infant is devoid of additional signs of systemic malperfusion. Injudicious use of bicarbonate to buffer this apparent deficit may lead to hypercapnia in an infant with marginal respiratory function in whom physicians are trying to avoid tracheal intubation. Also, immediate use of a silo has dramatically reduced the need for extensive fluid requirements as formerly used. Antibiotic therapy which typically begins with ampicillin and gentamicin can be changed to a first generation cephalosporin once perinatal infections are ruled out. The role of antibiotics at this point is to protect against omphalitis. When a fascial substitute is utilized there can be an intense cutaneous reaction of focal erythema with fever that often is limited to the initial 48 h and resolves spontaneously. The surgeon and intensivist should ensure that the erythema is not advancing and that there is no crepitus suggestive of a true infection as opposed to this inflammatory response. The abdominal compartment syndrome and discolored legs are a result of inadequate abdominal domain to accommodate the formerly eviscerated intestine. If pulmonary pressures are not excessive and renal function is maintained, most infants can be supported during the early postoperative period. The identification and management of abdominal compartment syndrome is discussed elsewhere in this textbook.

The most common chronic complication of gastroschisis is an adynamic ileus with dysmotility. Consequently, secure long term central venous access is obtained in the intensive care unit at the time of admission or preferably at the time of definitive abdominal wall closure. Umbilical access can be utilized early but often becomes dysfunctional secondary to the expanding ring on the silo. Simple peripheral access or peripherally inserted central catheters (PICC) can be utilized in the early period.

Once abdominal wall closure is complete, the anticipated course includes persistence of intestinal dysmotility with intolerance of oral feeds. Molik and colleagues reviewed 103 infants with gatroschisis at the J.W. Riley Hospital for Children and determined that the average time to resumption of full oral feeds was 22 days [20]. Late complications that require a high index of suspicion include abdominal catastrophes. In an infant with gastroschisis an acute abdominal inflammatory process may represent necrotizing enterocolitis (NEC) [21, 22] while an acute obstructive process could be secondary to segmental or complete midgut volvulus [23] or a missed mucosal web. The presentation of NEC is similar to that seen in the term newborn with an insidious onset and no well defined prodrome or pneumatosis on radiographic images. As with the preterm infant, antibiotics, gastric decompression, parenteral nutrition, and bowel rest are the mainstay of therapy. By definition, failure of the intestine to return to the abdomen during fetal development leaves the child with a rotational anomaly once the viscera are reduced *en mass* during the index surgical closure of the abdominal wall defect. This can raise a diagnostic dilemma in the postoperative period when the infant manifests a bowel obstruction. In an otherwise well child with gastroschisis who has a bowel obstruction, any cardinal signs of ischemia such as peritonitis, tachycardia (after appropriate resuscitation), fever, or leukocytosis should prompt surgical re-exploration. The current survival for infants with gastroschisis is 90 %.

Giant Omphalocele

Giant omphalocele is also a defect of the anterior abdominal wall, different from gastroschisis in that the defect is truly transumbilical, extending cephalad with the amnion and peritoneum typically preserved as a natural covering for the herniated contents (Fig. 9.2). Giant omphalocele is a truly

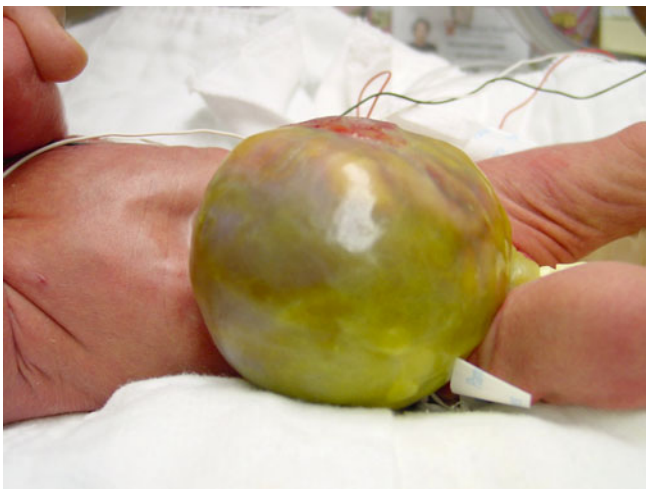

Fig. 9.2 Photo of 36 week preterm infant with a giant omphalocele. Note the amnion is intact, completely covering the herniated viscera

uncommon lesion. However, it poses unique management issues due to associated anomalies/syndromes and limited opportunity to perform early surgical closure.

Initial management requires placement of the infant (legs and abdomen) in a Lahey bowel bag and aggressive resuscitation as outlined previously for gastroschisis. Even if the amnion is intact initial evaporative losses can be extensive requiring plastic coverage until surgical consultation is available. A systematic review should be completed since omphalocele may be associated with other syndromic abnormalities including Beckwith-Wiedemann syndrome (gigantism, macroglossia, and hypoglycemia), imperforate anus, chromosomal abnormalities (Trisomy 3, 18 and 21), as well as renal and cardiac anomalies including the Pentology of Cantrell.

Although silo reduction may be performed for small omphaloceles, giant lesions require initial topical therapy to allow for chronic epithelialization of the sac covering the protuberant viscera. Methods to facilitate this include painting the sac with silver nitrate or silver sulfadiazine [24]. The use of Betadine has largely been abandoned due to the frequency of secondary hypothyroidism [25]. Similarly, using mercurochrome as an escharotic agent has been abandoned because of the fear of mercury poisoning [26]. Repair of the resultant ventral hernia is accomplished in stages at a later date. Use of collagen sheets to fill the ventral defect and advanced plastic surgical reconstruction [27, 28] has been suggested however, long term results are not yet available to evaluate whether these methods will be enduring.

When diaphragmatic and sternal defects are present, there is often associated pulmonary hypoplasia that will mandate chronic ventilation. The need for assisted mechanical ventilation is a poor prognostic indicator [29, 30]. Prior to consideration of tracheostomy, imaging with MRI should be undertaken in the stable infant. This will identify those with undiagnosed defects of the sternum, pericardium and central tendon of the diaphragm. Often repair of the omphalocele may be staged with chest coverage being a priority. Consequently premature tracheostomy can lead to an increased incidence of sternal infectious complications. Once the decision is made to forego early surgical intervention, tracheostomy can be performed if necessary. Oral feedings are often well tolerated. If associated anomalies complicate oral feeding or if chronic ventilation is required, nasoenteral access is preferable to allow early feedings.

Esophageal Atresia with and Without Tracheoesophageal Fistula

Esophageal atresia results from incomplete formation of the esophagotracheal septum during foregut development. Esophageal atresia occurs in 1:5,000 live births with approximately 86 % having a distal tracheoesophageal fistula [31]. The classification and incidence of TEF is:

1. Pure Esophageal Atresia, no Tracheoesophageal Fistula (7 %)
2. Esophageal Atresia with distal Tracheoesophageal Fistula (86 %)
3. H type Tracheoesophageal Fistula, no Esophageal Atresia (4 %)
4. Esophageal Atresia with proximal Tracheoesophageal Fistula (3 %)
5. Esophageal Atresia with double fistula (<1 %)

Prenatally, esophageal atresia is often not identified and only suspected in those with polyhydramnios. The postnatal presentation typically includes respiratory distress with initial feedings associated with excessive drooling or salivation. Often the initial symptom may be frequent vomiting. An inability to pass a nasogastric or orogastric suction catheter is often diagnostic.

In order to diagnose/manage this anomaly, the physician should carefully pass an orogastric tube into the proximal pouch typically meeting resistance at 8–10 cm. If an inability to discern between coiling in the mouth and appropriate passage into a blind ending esophagus is encountered, a nasogastric tube may be more easily passed directly into the esophagus. The infant should be kept with head of bed elevated to 45°. A chest radiograph confirms the diagnosis revealing the tip of the tube in a dilated, air-filled proximal, atretic pouch. Distal bowel gas confirms the presence of a tracheoesophageal communication, most commonly a distal fistula. Since 93 % of those with esophageal atresia have a tracheoesophageal fistula, any infant in respiratory distress should be considered a candidate for early tracheal intubation rather than continuous bag and mask ventilation. This will limit gastric distention and possible perforation [32]. If respiratory distress requires tracheal intubation, a tracheal

tube placed just proximal to the carina with the bevel aimed anterior will best avoid ventilation directly into the fistula [33, 34]. Similarly, aggressive abdominal palpation should be avoided as this could lead to reflux of gastric content into the fistula and direct aspiration.

As with any newborn, attention should be directed toward identification of associated anomalies [35]. Infants with syndromic features should have genetic screening for possible trisomies, most often Trisomy 18. Furthermore, patients with esophageal atresia and tracheoesophageal fistula require 2-D echocardiography, a renal ultrasound, and a lumbar ultrasound for surveillance of associated vertebral, anal, cardiac, tracheal, esophageal, renal, and limb (VACTERL) anomalies. Specifically, the echocardiographer should comment on the location of the aortic arch and continuity of systemic venous return. These items will dictate the surgical approach (right or left hemithorax) and also determine if the azygous vein can be safely sacrificed to facilitate dissection of the fistula.

Rarely does gastric distention become so great that it presents a severe risk of aspiration and profound chemical pneumonitis. However, if surgical consultation is not available, the stomach may be aspirated with a large bore angiocatheter [36]. Additionally in the preoperative period, most patients can be successfully maintained on conventional ventilation. Occasionally, it may become difficult to maintain ventilation due to a high output fistula (excessive ventilation through the fistula). Although immediate surgical intervention to ligate the fistula seems appealing, this approach carries tremendous morbidity and mortality. Described methods to improve ventilation and control the fistula have included: immediate right mainstem intubation, high frequency oscillation [37–39], transabdominal occlusion of the lower esophagus [40–42], gastrostomy tube with PEEP applied to the tube by immersion under 2–5 cm of water [43], transthoracic ligation of the fistula, and transtracheal balloon occlusion of the fistula [44–46]. Our group favors Fogarty balloon occlusion of the fistula. With the distressed neonate remaining in the neonatal unit, beside fluoroscopy is obtained. A 3 French Fogarty with 1–2 mL of contrast in the balloon is passed along side the endotracheal tube. First the catheter is directed by laryngoscopy and then guided with fluoroscopy. Direct midline passage of the catheter to the level of the diaphragm confirms placement into the fistula. Occlusion of the balloon immediately controls the fistula and improves respiratory function (Fig. 9.3).

Surgical management is beyond the scope of this chapter however in general, those with pure esophageal atresia and no fistula undergo early elective gastrostomy with delayed repair at 3 months. Infants with esophageal atresia and a fistula undergo semi-urgent repair in the newborn period. The rare group with an *H* type fistula and no esophageal atresia often present later in life with episodic choking spells, respiratory distress or recurrent pneumonias.

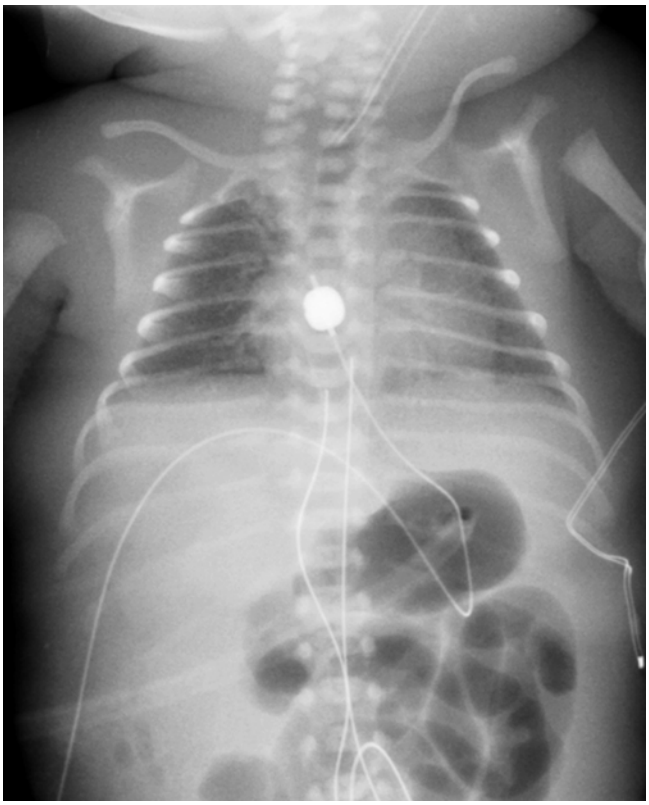

Fig. 9.3 Chest radiograph of a newborn infant with Type C esophageal atresia and distal tracheoesophageal fistula. The newborn in respiratory distress may be treated with a fogharty catheter, in this case placed retrograde adjacent to the gastrostomy tube, allowing occlusion of a high output fistula (see balloon with contrast)

The postoperative care of patients with esophageal atresia and tracheoesophageal fistula warrants a few special considerations. Acceptable reintubation rates in the general NICU population approximate 15–30 % [47, 48]. For TEF, the timing of postoperative extubation is particularly pertinent. Avoiding postoperative reintubation minimizes the chances of traumatic injury to the surgical repair. We would recommend postponing extubation until the infant no longer requires opiates for post surgical pain management. If required, the most experienced personnel available should perform reintubation since inadvertent injury to the tracheal fistula or accidental esophageal intubation could be catastrophic. Immediate respiratory failure following extubation can result from breakdown of the fistula closure or, more commonly, from tracheomalacia. Leakage from the fistula is typically noted prior to extubation based on the infant's response to weaning of ventilation, chest tube output (air leak) and serial chest radiographs. Tracheomalacia responds favorably to continuous positive airway pressure (CPAP) via nasal prongs. Concerns regarding the use of CPAP are unfounded if one considers that first the fistula has already been surgically closed and second, normal intraesophageal pressure with swallowing exceeds pressures typically

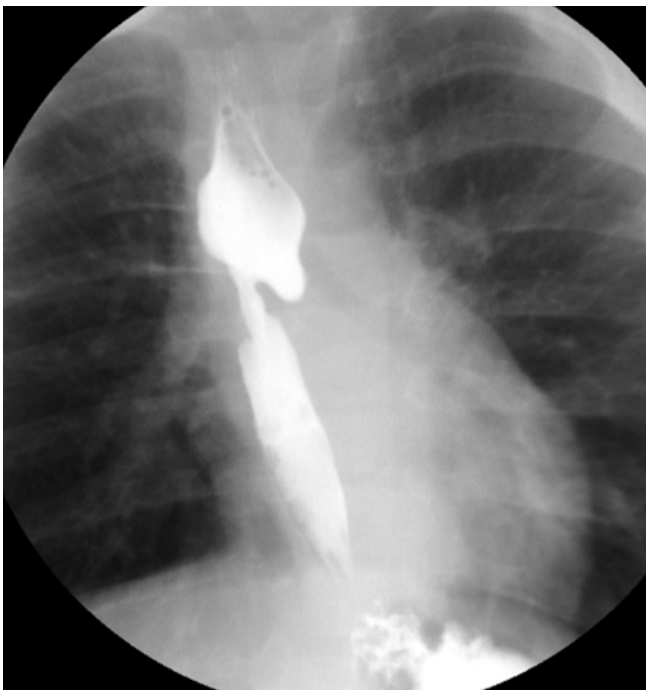

Fig. 9.4 Contrast esophagram 1 week following surgical repair of esophageal atresia with distal tracheoesophageal fistula demonstrating an anastomotic narrowing and ballooning of the proximal esophageal segment

prescribed for CPAP in an infant. An expanded algorithm to evaluate and manage tracheomalacia can be found elsewhere [49]. However, we routinely begin with rigid bronchoscopy while the infant is breathing spontaneously. If there is true tracheomalacia due to maldevelopment of the tracheal cartilage, chronic CPAP or even tracheostomy may be required. Certainly repeated episodes of obstructive apnea in a patient with known tracheomalacia should prompt evaluation for possible aortopexy [50–52] or tracheostomy. If tracheostomy is chosen, the tube must remain at least 1–2 cm above the carina. A tube in this location will functionally stent the trachea and also prevents impaction of the distal tracheostomy tube into the *pit* from the original fistula.

The transanastomotic feeding tube allows nasogastric feeds to begin on postoperative day 2 or 3. Low volume, continuous drip feeds are helpful in avoiding reflux. At 1 week following surgery a contrast swallow is obtained to evaluate for patency and anastomotic leak. Almost always there is anastomotic narrowing with proximal dilation (Fig. 9.4). If the contrast study confirms adequate patency of the anastomosis, devoid of any leak, oral feedings can be initiated. Strictures are managed with bougie dilation under fluoroscopic guidance or balloon dilatation. Anastomotic leaks are typically well contained and are optimally managed with an additional 1–2 weeks of nasogastric feedings. Small anastomotic leaks almost uniformly close spontaneously. Anastomotic disruption is a very rare complication characterized by large losses of saliva recovered in the thoracostomy tube and verified by contrast esophagram and will often require re-operation.

Finally in a review of 227 infants with esophageal atresia with or without a tracheoesophageal fistula managed at the J.W. Riley Hospital for Children, up to 58 % of children developed symptomatic gastroesophageal reflux (GERD) [53]. Most patients can be treated or temporized with histamine receptor blockade and motility agents often in concert with continuous drip feeds if necessary. Ultimately however, nearly half of those with GERD following repair of esophageal atresia will require a surgical anti-reflux procedure [53]. The subset of patients with pure esophageal atresia has a higher incidence of GERD. In addition, often the presenting symptom in this group is a sudden death spell or acute life threatening event (ALTE). Given the devastating consequences of an arrest at home, those with pure esophageal atresia who develop significant reflux after the initial repair should be considered for early fundoplication. In those with known ALTE's this may mandate surgical repair prior to discharge even if this strategy requires prolonged hospitalization.

Congenital Diaphragmatic Hernia

Since the original description of a successful repair in 1946 by Gross [54], volumes have been written about the management of congenital diaphragmatic hernia (CDH). Initially, investigators focused on the timing and methods for reduction of herniated viscera. In the past two decades, increased understanding of the pathophysiology concerning this lesion has directed our focus toward managing the attendant pulmonary hypertension and pulmonary hypoplasia [55–57]. This emphasis has proven pivotal and resulted in the only significant improvement in mortality since the time of Gross. More recent investigations have highlighted how surfactant deficiency/dysfunction [58] and associated cardiac anomalies [59] further compromise these infants.

With improving prenatal care, most CDH lesions are diagnosed in the antenatal period by maternal ultrasound, often detectable on the index sonogram at 16 weeks gestation. Antenatal identification has improved the ability to predict outcomes in the antenatal period and has improved survival in some scenarios [60–62]. The incidence of CDH is one in 4,000 live births. Congenital CDH defects are either posterolateral, (Bochdalek hernia) or anterior parasternal (Morgagni hernia) with the left-sided Bochdalek hernia predominating in 80–90 % of affected infants. Left-sided hernias allow herniation of hollow viscera into the thoracic cavity including the stomach, small and large bowel as well as intra-abdominal solid organs most commonly spleen and liver. In right-sided hernias, only the liver and a portion of

the large bowel tend to herniate. Bilateral hernias are uncommon and usually fatal. Nearly 50 % of patients have associated anomalies including congenital heart disease, renal anomalies, intestinal atresia, malrotation, and neural tube defects [59]. Lethal anomalies are present in up to 16 % of infants. While CDH is most commonly a disorder of the newborn period, as many as 10 % of patients may present after the newborn period and even during adulthood.

Although bronchogenic cysts, neonatal diaphragmatic eventration, and congenital cystic adenomatoid malformations can present with similar findings, the prenatal history, physical examination and postnatal radiographic findings can almost always confirm the diagnosis. The outcome from CDH is largely dependent on the degree of pulmonary hypoplasia and any associated pulmonary hypertension. Consequently, nearly all infants (95 %) will have immediate respiratory distress upon delivery. At birth, examination is immediately notable for a scaphoid abdomen, diminished or absent breath sounds on the affected side with displacement of the heart sounds to the contralateral side.

Once the diagnosis is achieved, stabilization of the infant is critical. In general, bag-valve-mask ventilation with a face-mask should be avoided, if possible. Instead, immediate tracheal intubation in the delivery room should be performed to minimize gaseous distention of the bowel, some of which resides in the chest and can further compromise the ventilatory status. In addition to establishing a secure airway and peripheral venous access, placement of an orogastric tube prior to the chest radiograph helps determine the position of the stomach. Typical findings in left-sided posterolateral CDH include air- or fluid-filled loops of the bowel in the left hemithorax and shift of the cardiac silhouette to the right (Fig. 9.5). Although controversy exists, most accept that infants with known lesions require immediate intubation and should initially be oxygenated with 1.0 FiO_2 until stabilized at a receiving center. Peak inspiratory pressures can often be maintained below 30 cm H_2O, adequate to obtain chest expansion. The orogastric sump tube should be placed to continuous suction and frequently assessed. Even if the amount of draining succus is minimal, continuous suction evacuates swallowed air preventing gaseous distention of intestinal contents herniated into the chest. No attempts should be made to assess arterial blood gases prior to evaluation in the referral center with neonatal specialists and pediatric surgical support. Pulse oximetry and venous blood gases are adequate initially. Once fully evaluated at the referral center, a secure preductal arterial line in the right radial artery is optimal in conjunction with pre- and post-ductal pulse oximetry.

The incidence of associated cardiac anomalies often exceeds 25 %. Consequently, echocardiography should be performed to evaluate for associated congenital heart disease, with specific evaluation for aortic arch anomalies as well.

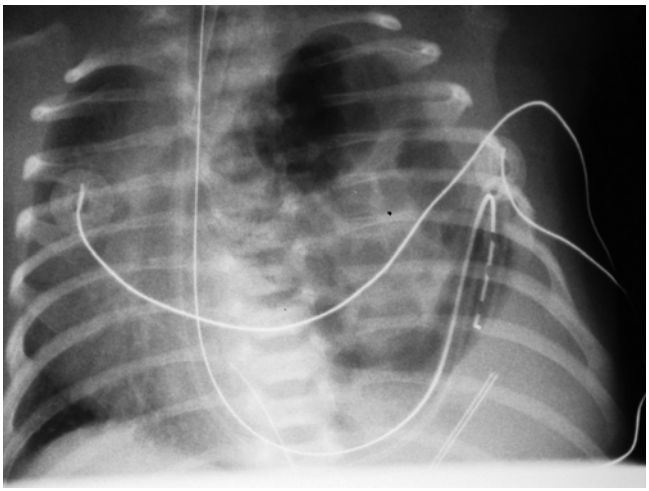

Fig. 9.5 Chest radiograph of a newborn with congenital diaphragmatic hernia. The orogastric tube extends through the diaphragmatic defect and into the left pleural space

Similarly, renal and cranial ultrasonography should be obtained to evaluate for genitourinary anomalies and intracranial lesions or bleeding, particularly if the infant is being considered for extracorporeal support (ECMO).

Once at a defined treatment center, the subtleties of management may be pursued. The goals of managing associated pulmonary hypertension and pulmonary hypoplasia are optimizing oxygenation while avoiding barotrauma. High frequency oscillation is particularly useful in providing adequate ventilation while minimizing barotrauma. Another option for assisted ventilation is to allow the infant to breathe spontaneously with any synchronized mode of ventilation [63]. The flow-triggered mode limits delivered pressure but can match the spontaneous effort of tachypneic newborns [63]. The ultimate goal is to avoid ventilator-induced lung injury to the viable parenchyma (barotrauma). This strategy often requires permissive hypercapnea. Although hypercapnia is a stimulus for pulmonary vasoconstriction this effect is limited if the pH is maintained >7.20. Peak inspiratory pressure <25–30 cmH_2O, while delivering a tidal volume of up to 5 mL/kg is optimal. PEEP is slowly increased to help maintain appropriate oxygenation. Preductal oximetry >90 % is adequate despite FiO_2. Infrequent doses of sodium bicarbonate at 0.5–2.0 mEq/kg can buffer acidemia. Progressive or persistent acidemia (respiratory or metabolic) requiring peak inspiratory pressures >30 or hypoxemia with the FiO_2 at 1.0 suggests alternative ventilation strategies such as high frequency oscillating ventilation (HFOV) or ECMO may be required [64]. Adjuncts including surfactant therapy and inhaled nitric oxide are known to theoretically replace deficient levels of surfactant and reduce right ventricular work respectively. Unfortunately, neither has been proven to limit the need for ECMO in controlled studies [65, 66]. Persistent hypoxemia with hemodynamic instability is

also an indication for rescue with ECMO. In this scenario, appropriate but judicious use of intravenous fluids are used to restore hemodynamic stability, keeping in mind that in this particular subset of patients, pulmonary function is sensitive to volume overload. As previously noted, early echocardiography allows for assessment of congenital defects including aortic arch anomalies prior to initiation of ECMO. Echocardiography may also be used to assess and reassess left ventricular end diastolic volume, right ventricular dysfunction, septal shifting, and as an indirect assessment of pulmonary pressure. Given the degree of relative acidemia and hypoxemia in the complicated infant with CDH, echocardiography is often the best guide for fluid resuscitation.

Adjuncts to this critical management include a minimal stimulation environment including strategic but limited endotracheal suctioning. If stable infants require continuous sedation, we prefer ativan and fentanyl or morphine. Routine intracranial ultrasounds are performed before and after initiation of ECMO to evaluate for intraventricular hemorrhage. Edema is common as an early secondary complication from the systemic inflammatory insult created by the ECMO circuit. Oliguria and renal failure are not uncommon as well. Again, liberal use of echocardiography helps establish appropriate circulating intravascular volume.

Surgical repair of the diaphragmatic defect is well described elsewhere [67], but in general operative intervention occurs when the infant is stable and ready to be weaned from ECMO. The repair is performed by primary closure of the diaphragmatic tissue or with the assistance of a bioprosthetic patch. In children on ECMO, a chest tube is frequently placed due the increased bleeding risk associated with the iatrogenic coagulopathy.

The postoperative management is dictated by the infant's response to initial therapy and surgical intervention. Aside from chronic pulmonary disease, infants with CDH often suffer from gastroesophageal reflux (GERD). As with any child with GERD, appropriate medical management is employed with surgical intervention reserved for refractory cases. Despite significant advances in critical management over the past decade, overall survival in neonates with CDH remains at 60–80 %. Unfortunately survivors often suffer chronic morbidity including that inherent to the disease and also morbidity introduced from treatment. As survivors from congenital diaphragmatic hernia continue to age, long term sequelae to their pulmonary, cardiac, gastrointestinal and neurocognitive development are more apparent [68–70].

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) occurs in preterm or low birth weight infants in 90 % of cases, with less than 10 % noted in term infants [71]. The etiology of NEC remains elusive however it is routinely characterized by mucosal or transmucosal necrosis of part of the intestine. The spectrum of potential outcomes includes partial or patchy ischemia with intestinal necrosis, perforation with pneumoperitoneum, abdominal or systemic sepsis, and panintestinal involvement which is almost always lethal. The regions of bowel most often affected are the right side of the colon and the distal ileum, although any portion of the bowel is susceptible including the stomach. Despite more effective management and preventive strategies, the gross incidence continues to increase because of the increased number of surviving preterm infants.

A common clinical scenario in NEC is mucosal injury due to mesenteric hypoperfusion typically in the setting of systemic sepsis. Other contributing factors include indwelling umbilical catheters (arterial), acidemia, hypoxemia, a patent ductus arteriosus, and indomethacin therapy [72, 73]. In addition, polycythemia, the use of hypertonic formulas, and early establishment of full enteral feedings or rapid advancement of feedings in preterm infants may lead to NEC or at least mucosal injury [74–77]. Center-wide epidemics of NEC are documented, and have been linked to various infectious agents including *Clostridium perfringens*, *Escherichia coli*, *Staphylococcus epidermidis*, and rotavirus. Although NEC is quite morbid for these critically ill preterm infants, appropriate management maintains overall mortality rates less than 20 % [78, 79]. If management requires surgical intervention, operative mortality may be as high as 50 %.

Onset occurs 2 weeks to several months after birth. Meconium is usually passed normally, and the initial signs of NEC include atypical apnea/bradycardia, abdominal distention and gastric retention of succus or feedings. Frankly bloody stool is observed in approximately 25 % of patients. The onset of NEC can be insidious, and sepsis may occur hours before any intestinal abnormality is noted. Early progression of NEC may be rapid but often plateaus after 72 h. Although focal pneumatosis on abdominal radiographs is often a relatively early finding, diffuse pneumatosis and anterior abdominal wall erythema are late findings, typically indicative of transmural intestinal necrosis. The presence of irritability, poor feeding (increased gastric residuals), abdominal distention, and dilated bowel loops on abdominal radiographs, especially when associated with bloody stool, is highly suspicious of NEC. These findings should prompt preemptive measures until the diagnosis is excluded.

In any infants suspected of having NEC, periodic radiography of the abdomen that includes a routine frontal abdominal view (Fig. 9.6a) and a lateral decubitus image (Fig. 9.6b) is prudent. Some centers prefer a supine cross table lateral view (Fig. 9.6c). A KUB with left lateral decubitus is generally preferred, as these are equally sensitive in identifying free intraperitoneal air, but have the added benefit of isolating

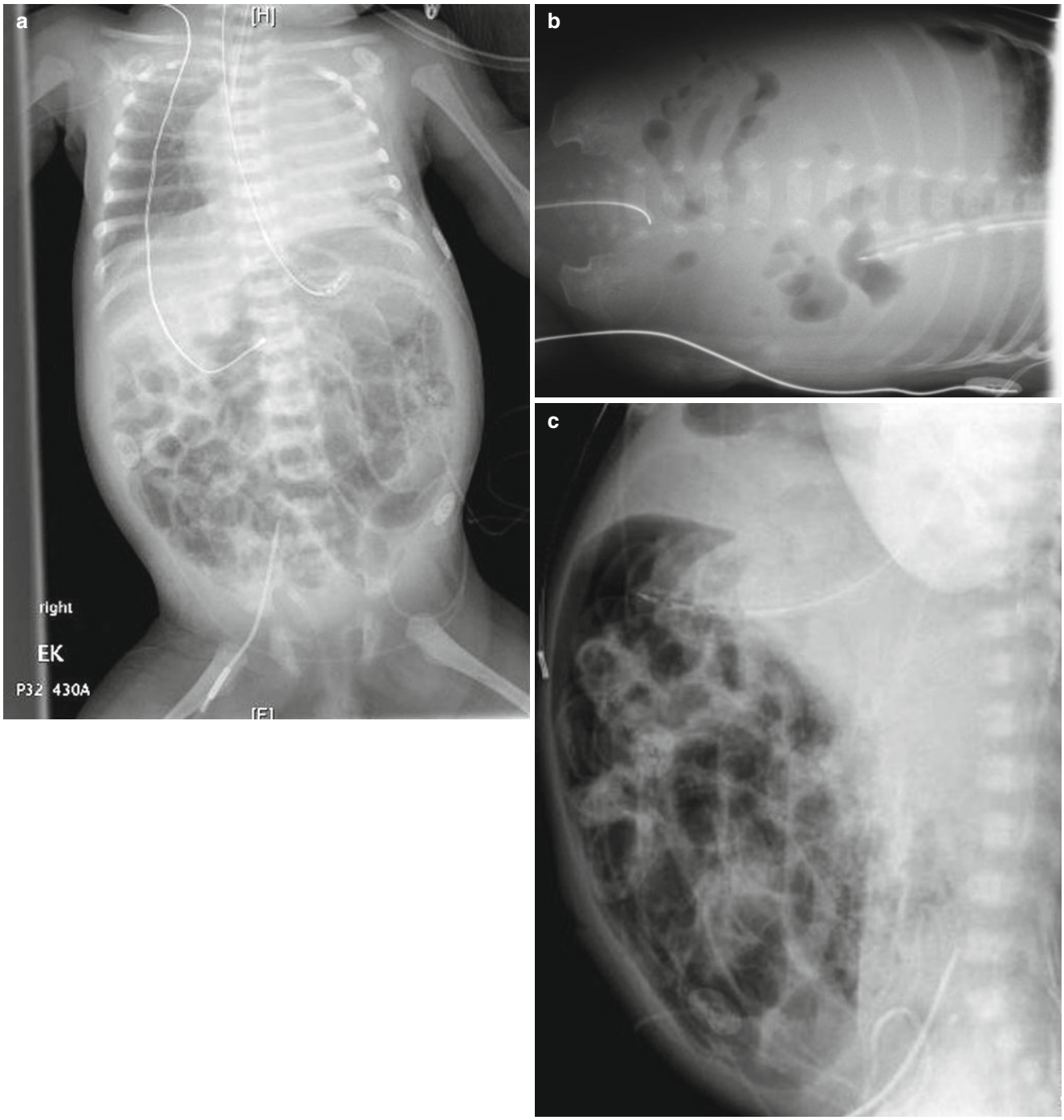

Fig. 9.6 Radiographic evidence of necrotizing enterocolitis as demonstrated by a KUB (**a**), left lateral decubitus (**b**), and cross-table lateral radiograph (**c**). Left lateral decubitus abdominal radiograph of a preterm infant, revealing a small pocket of "free air" (pneumoperitoneum) adjacent to the liver and right diaphragmatic sulcus

fixed loops of bowel that are suggestive of significant intestinal injury in a neonate that is unresponsive to medical management. Abdominal radiographs should be obtained every 6–8 h initially. Immediate bowel rest with orogastric decompression and broad spectrum antibiotic therapy can help prevent fulminate involvement (usually ampicillin, gentamicin and the addition of clindamycin if the neonate has been formerly introduced to feedings). Electrolytes and platelet count are routinely monitored every 8–12 h as well. Possible indications for operative intervention include progressive hemodynamic instability and acidemia, abdominal wall cellulitis or erythema, a fixed loop on serial radiographs, portal venous air (Fig. 9.7a), or free intraabdominal air (pneumoperitoneum) (Fig. 9.7b).

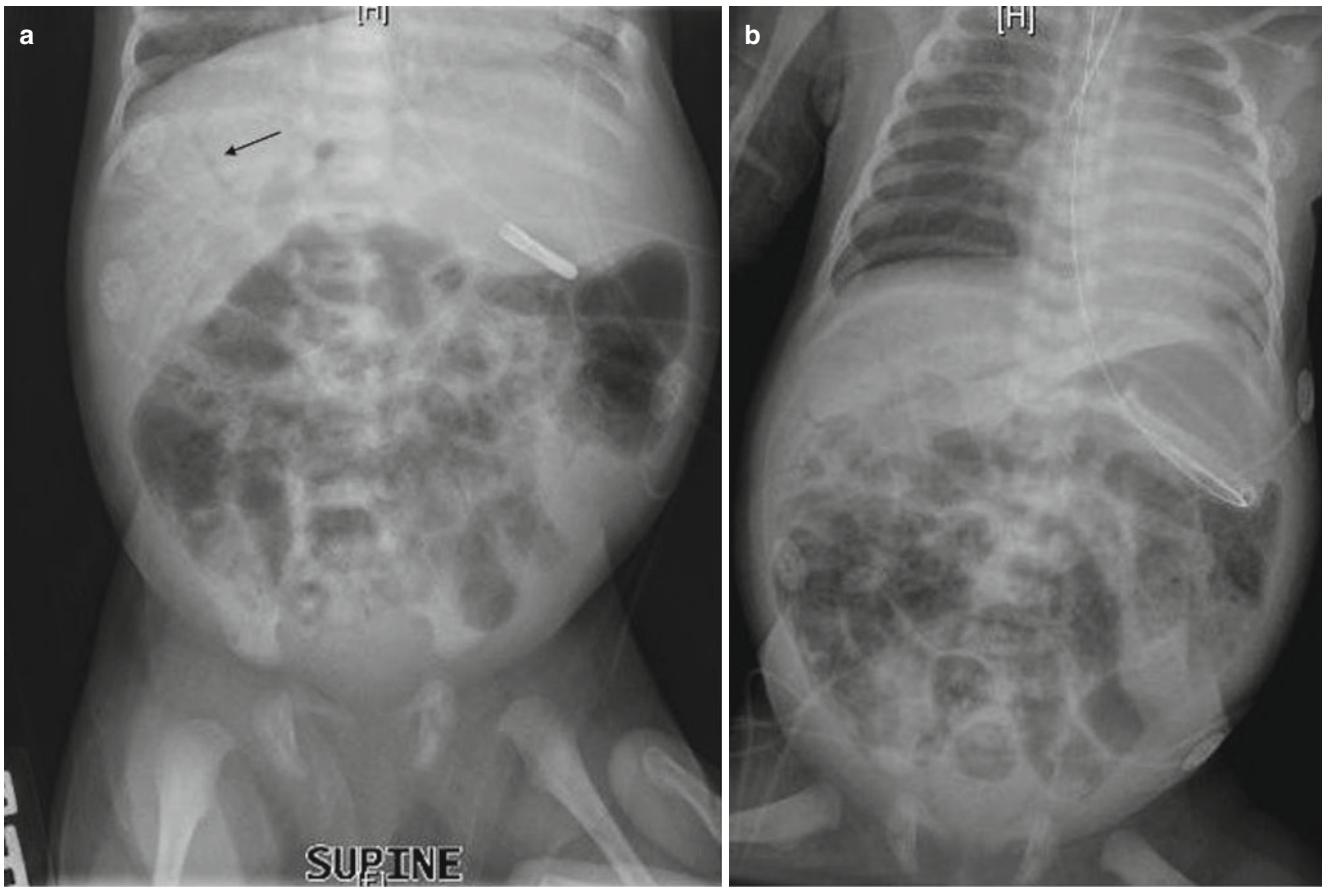

Fig. 9.7 Radiographic evidence of necrotizing enterocolitis suggesting need for surgical exploration, including portal venous air (**a**) (*arrow*) and free air (**b**)

Morbidity in an infant treated for NEC includes intestinal stricture(s), peritoneal adhesions with obstructive symptoms, and bowel perforation. If perforation occurs, surgical exploration is mandated. Resection of frankly ischemic segments follows with the rationale of maintaining intestinal length. In order to avoid unnecessary resection of intestine, segments are often excluded and re-examined with repeat laparotomy in 48–72 h. Extensive resections of bowel may result in short-bowel syndrome. Preterm infants larger than 1,000 g that demonstrate evidence of NEC rather than an isolated perforation will undergo surgical therapy that typical includes laparotomy with limited resection and ostomies. Neonates with very low birth weight (less than 1,000 g) often undergo bedside percutaneous peritoneal drainage. Even when perforation is confirmed during bedside drainage, only 30 % will ultimately require laparotomy for stricture, obstruction or persistent sepsis [80–82].

Thorough resuscitation should begin with isotonic fluids and blood products as required. Parenteral nutrition will be the mainstay of support for those neonates that require surgical intervention. Even in neonates given distal ostomies, the ability to maintain full nutritional support with enteral feeds is limited. Consequently, early acquisition of central access for parenteral nutrition helps avoid premature resumption of enteral feeds. Often surgical procedures result in proximal ostomies. Refeeding of the proximal effluent into the distal ostomy is an attractive concept but can be complicated by injury to the distal stoma, fluid and electrolyte disturbances and cutaneous breakdown around the distal stoma. In addition, this management is very labor intensive for nursing. The goal of postoperative nutritional support is adequate weight gain, with proportionate somatic growth, prior to consideration of ostomy reversal. Colonic strictures have been observed in 15 % of patients following initial successful medical management of NEC. Consequently, a distal contrast enema or antegrade contrast study via the distal stoma is mandatory prior to embarking on closure of the stoma. Post-operative patients with NEC that are not nutritionally optimized and have sustained early TPN-related cholestatic changes present the greatest challenge. The authors find routine monitoring of weight and serum prealbumin (preferably >10 ng/dL) are the most sensitive indicators of nutritional restoration. In those infants that cannot achieve these goals, the intensivist should anticipate a need for extensive blood products during and after the ostomy reversal. Often this second operation can have morbidity

equal to that of the index illness. Coagulopathy, abdominal compartment syndrome and acute renal failure are complications that are not infrequently observed in the immediate postoperative period following stoma reversal. We employ liberal use of blood products, particularly platelets and fresh frozen plasma, in conjunction with aggressive fluid resuscitation prior to any use of vasopressive and/or inotropic agents. In addition to adequate visceral protein levels, it is important to remember that a bowel anastomosis requires adequate circulation and oxygenation to heal, emphasizing the importance of appropriate resuscitation following the surgical procedure. Specifically, the mesentery is divided so that circulation to the anastomosis is dependent on end arterial supply. Consequently, thorough volume resuscitation and adequate hemodynamic support is necessary to prevent ischemia and the secondary anastomotic complications including leak and stricture. Survivors of NEC can be plagued by short bowel syndrome or intestinal dysmotility, however, this remains confined to a minority of patients as most will ultimately resume normal intestinal integrity and function.

Lymphatic Malformations

Historically termed cystic hygromas or lymphangiomas, cervical and thoracic lymphatic malformations can present unique challenges to the surgeon and intensivist. These slow-flow vascular anomalies of the lymphatic system that consist of localized or diffuse malformations of lymphatic channels best characterized as microcystic, macrocystic, or both. From primitive lymphatic channels, sacs are formed that establish drainage with the venous system. Failure to establish effective drainage to the venous system results in dilated disorganized lymph channels. When massively dilated these present as lymphatic malformations. Since they develop from budding lymphatics, these lesions may occur anywhere, most commonly encountered in the cervicofacial region, axilla/chest (70–80 %), mediastinum, retroperitoneum, buttock, and anogenital region [83]. Lymphatic malformations frequently abut or incorporate adjacent neurovascular structures.

Lymphatic malformations are often apparent at birth but as many as 30 % may not be evident until age 2. The masses are usually large, soft structures without clear margins. Airway obstruction is the most critical complication of these malformations occurring in the neck. To assess the risk of airway obstruction, the primary evaluation of children with lymphatic malformations should include inspection for any signs of tracheal deviation or airway involvement. Specifically, the initial examination should include a comprehensive examination of oropharynx, hypopharynx, larynx, and base of tongue. This often requires flexible laryngoscopy. In any patients with a high risk of obstruction, the airway should be secured with endotracheal intubation. Only experienced personnel should attempt intubation in this scenario. If direct visualization is limited, flexible or rigid bronchoscopy may facilitate endotracheal tube placement. Intralesional hemorrhage occurs in up to 13 % of patients. Accordingly, any infant with a painful, enlarging lesion with or without distinct evidence of acute blood loss should be considered for airway stabilization.

Routinely, a chest radiograph is obtained to establish the presence of mediastinal involvement. Ultimately magnetic resonance imaging (MRI) is optimal to evaluate the full extent of invasion including delineation of regional neurovascular structures. CT scan is not as effective in delineating soft tissue involvement, particularly with the fine detail required prior to head and neck dissections. Some lesions are detected on prenatal ultrasound. If a lesion detected in the prenatal period is associated with tracheal compression, a planned ex-utero intrapartum treatment (EXIT) procedure is often the only lifesaving measure (Fig. 9.8). The infant is delivered via planned cesarean section wherein bronchoscopic confirmation of endotracheal access is confirmed or tracheostomy is performed prior to separation of the infant from placental support.

Surgical excision remains the optimal therapy in many cases. However, increasing use of sclerotherapy which works through obliteration of the lymphatic lumen with further sclerosis and fibrosis. OK 432, a lyophilized preparation of a streptococcal toxin is being utilized, particularly in regions where dissection carries tremendous morbidity such as the floor of mouth or hypopharynx. This induces a significant local inflammatory response with fibrosis, and has demonstrated success with shrinkage of lymphatic tissue [84]. Although this is an attractive alternative, sclerotherapy with OK 432 has been limited to investigative trials only. Since surgical excision is the mainstay of therapy, the goal for surgical therapy is complete extirpation when possible. The excision is never radical preserving crucial neurovascular structures. For this reason surgical intervention may be delayed in premature infants or for lesions that may require difficult repairs. Surgical resection may be quite involved, often requiring an extensive neck dissection or a median sternotomy for mediastinal extension.

Complications resulting from excision of a lymphatic malformation include damage to adjacent neurovascular structures, chylous fistulae, chylothoracies, and bleeding. Of these, chylothorax is typically problematic after excision of large lesions, particularly those with thoracic involvement. Chronic high volume drainage can have adverse consequences on immunity and nutrition. The effluent can be evaluated for lymph by checking triglyceride level and total cell count. Triglycerides greater than 100 and a predominance of lymphocytes confirm the effluent as lymph rather than serous

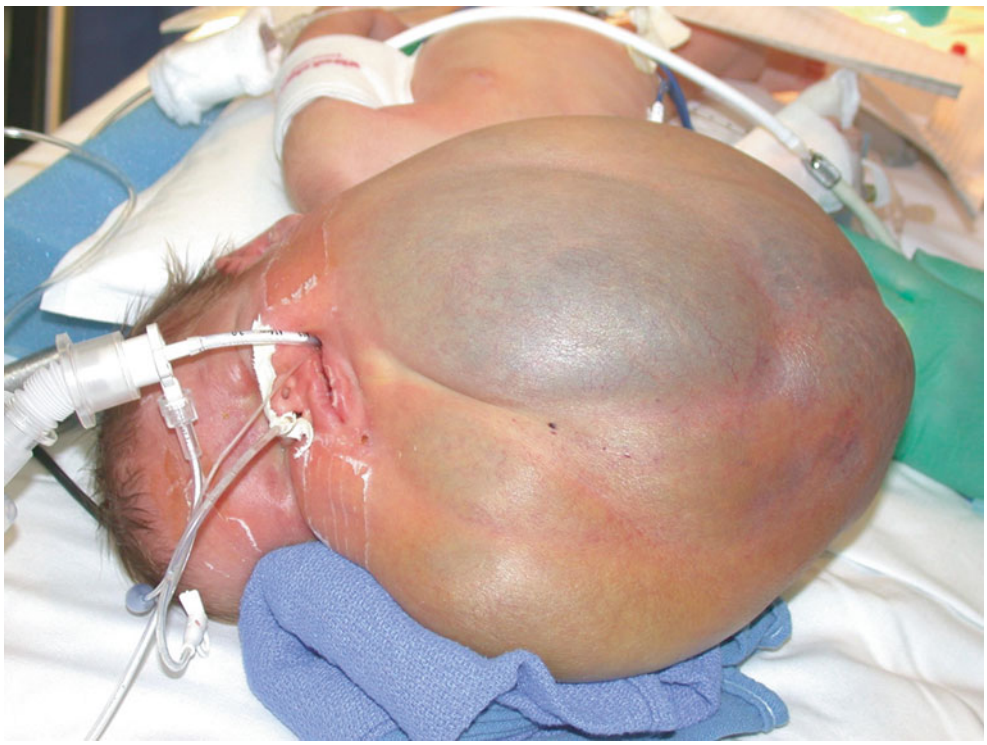

Fig. 9.8 Photo of newborn with a massive cervical cystic hygroma. Concern for airway compromise prompted *ex-utero intrapartum treatment* (EXIT procedure) to secure the airway prior to eliminating placental support

fluid. Often accumulation can occur in the pleural space which introduces the added complication of respiratory embarrassment. Persistent chylous effusions can be managed by low fat feedings followed by reexploration for surgical ligation of lymphatic channels or pleural-peritoneal shunting of accumulated lymph [85].

Intestinal Obstruction

Intestinal obstruction in infants or children results from abnormalities in rotation, innervation, recanalization or luminal obstruction with most presenting during infancy. Common signs that raise suspicion for intestinal obstruction in the neonate include an antenatal history of polyhydramnios, bilious (green) emesis, abdominal distension and failure to pass meconium in the first 24 h of life. Almost uniformly problems are initially called to the attention of the intensivist by nursing personnel who describe feeding intolerance. In the newborn or critically ill child, bilious emesis is rarely a benign observation. Subsequent physical examination reveals varying degrees of abdominal distention. Gastric decompression (by passing an orogastric tube) is paramount in any ill infant or child with abdominal distention or vomiting. A flat abdominal radiograph with left lateral decubitus views will help ascertain the level of obstruction. Caution should be used in attempting to reliably differentiate small from large intestine in the neonate based on the plain radiographs. The purpose of plain radiographs in the infant is to recognize intestinal dilatation and define proximal from distal obstruction. This will then prompt appropriate contrast studies if indicated. The contrast study will indicate whether the dilated intestine is small bowel or colon, identify instances of unused colon (microcolon), and locate the position of the duodenum and cecum to evaluate for anomalies of rotation and fixation.

In any infant or child being evaluated for emesis or intestinal obstruction, caretakers must keep in mind that the problem may be *non-surgical*. Sepsis of the newborn with associated ileus is the most common cause of non-surgical bilious vomiting and abdominal distention. Intracranial lesions including hydrocephalus and subdural hemorrhage can also lead to ileus. Renal disease or urinary tract anomalies with associated uremia and severe hydronephrosis may present with abdominal distention and vomiting.

Proximal obstructions can result from malrotation, annular pancreas, duodenal atresia, duodenal stenosis, duodenal web, antral web and a preduodenal portal vein. Distal obstructions include anorectal malformations, meconium plug syndrome, meconium ileus, intestinal atresias (ileal or colonic), small left colon syndrome and Hirschsprung's disease. Below we highlight those lesions that warrant particular care in the perioperative period.

Proximal Obstructions: Malrotation

Rotational anomalies of the alimentary tract often do not require intensive management unless the outcome is catastrophic as seen with complete midgut volvulus. This lesion

warrants emphasis in that any newborn infant who vomits bile or has bilious drainage from an orogastric tube should receive prompt surgical evaluation and immediate radiographic studies if possible. Malrotation of the intestine results from interruption of the normal embryologic regression of the intestinal loop from an extracoelomic position in the antenatal period and further interruption of subsequent fixation. Malrotation is an all encompassing term but truly is a group of disorders that include non-rotation, reverse rotation (causing obstruction or reversal of the normal duodenal/SMA relationship), and true malrotation (most often associated with malfixation). Malrotation predisposes patients to two problems: midgut volvulus and small bowel obstruction. Complete midgut volvulus may occur because the proximity of the cecum to the duodenum is associated with a narrow stalk at the base of the mesentery about which the viscera may torse. The accompanying vascular compromise of the superior mesenteric vessels creates a potentially lethal ischemic insult. The acute mortality from midgut volvulus is almost 15 % while those that survive frequently have short bowel syndrome and are dependent on total parenteral nutrition (TPN). In infants, TPN-related cholestatic changes and resultant cirrhosis have an equally high mortality. Uniformly these children with short bowel syndrome require intestinal lengthening procedures or small bowel transplantion to survive. As for intestinal obstruction, most cases are not due to midgut volvulus but instead are a true mechanical obstruction from duodenal bands (Ladd's bands). The malrotated or incompletely rotated colon (cecum) finds itself located adjacent (medial) to the duodenum. Native attempts at retroperitoneal fixation create Ladd's bands which are abnormal peritoneal attachments from the cecum that cross the duodenum and pass to the undersurface of the liver or posterior abdominal wall. Of all children with rotational anomalies, 50 % present in the first month of life with 30 % in the first week [15]. Only 28 % have bloody stools [15]. Although malrotation is a condition predominantly noted in infancy, affected children may remain clinically "silent" and can present at any age, often manifesting as failure to thrive, chronic recurrent abdominal pain, incidental identification of chylous ascites during elective inguinal hernia repair, or diarrhea from malabsorption. Associated anomalies are present in approximately 60 % of patients. Aside from common congenital heart lesions, malrotation may be associated with heterotaxy, an abnormal arrangement of abdominal organs including the spleen, liver, right-sided or left-sided isomerism of the major blood vessels and an interrupted vena cava. Rotational anomalies are often present in patients with congenital diaphragmatic hernia, omphalocele and gastroschisis and are slightly more prevalent in patients with imperforate anus, duodenal atresia/web/stenosis, preduodenal portal vein, annular pancreas, and biliary atresia.

The diagnostic test of choice in a child with possible malrotation with or without midgut volvulus is an upper gastrointestinal contrast study (UGI). In most patients with malrotation, the UGI is easy to perform and relatively easy to interpret with a few notable exceptions. If the image reveals a complete duodenal obstruction, the UGI cannot differentiate between midgut volvulus and less emergent causes for proximal intestinal obstruction. If uncertainty exists, following the barium through to the colon ensures normal rotation, particularly if the cecum is noted in the right lower quadrant. Obviously volvulus is a true surgical emergency, whereas malrotation without midgut volvulus may be surgically treated, urgently, but at the next available elective setting.

Proximal Obstructions: Duodenal Atresia, Stenosis, and Webs

Duodenal atresia represents complete obliteration of the duodenal lumen. The duodenal diaphragm or web is thought to represent a mild form of atresia. Duodenal stenosis (incomplete obstruction of the duodenal lumen) is discussed with duodenal atresia because they represent a spectrum of similar intrauterine events. Annular pancreas occurs when pancreatic tissue surrounds the second portion of the duodenum. If the encirclement is complete, it may be associated with complete or incomplete duodenal obstruction. In general the relative incidences of these lesions are duodenal atresia (40–60 %), duodenal webs (35–45 %), annular pancreas (10–30 %) and duodenal stenosis (7–20 %). One third of the infants have anomalies of rotation and fixation.

Duodenal atresia occurs with an incidence of one per 6,000 births, with almost half of affected infants born prematurely. A maternal history of polyhydramnios will be present in 40 % of neonates with duodenal obstruction. As usual, an evaluation for associated anomalies and genetic disorders is essential. Duodenal atresia or stenosis is most commonly associated with trisomy 21, affecting 22–30 % of patients [15].

Infants with duodenal atresia often present with bilious vomiting in their first few hours of life, while patients with duodenal stenosis present at various ages. This presentation is not uniform. In particular, the emesis may be non-bilious if the web or atresia is proximal to the sphincter of Oddi. The clinical findings depend on the degree of stenosis. Occasionally, with duodenal webs or stenoses, presentation may be delayed and may even occur in adults.

In many instances this condition is now recognized during fetal life on prenatal sonography. In the other babies, plain abdominal radiographs will demonstrate the double bubble appearance (dilated stomach and proximal duodenum) with no distal gas characteristic of complete obstruction due to duodenal atresia (Fig. 9.9). Distal bowel gas indicates the presence of duodenal stenosis due to an incomplete membrane. Occasionally, a radiograph obtained with the patient

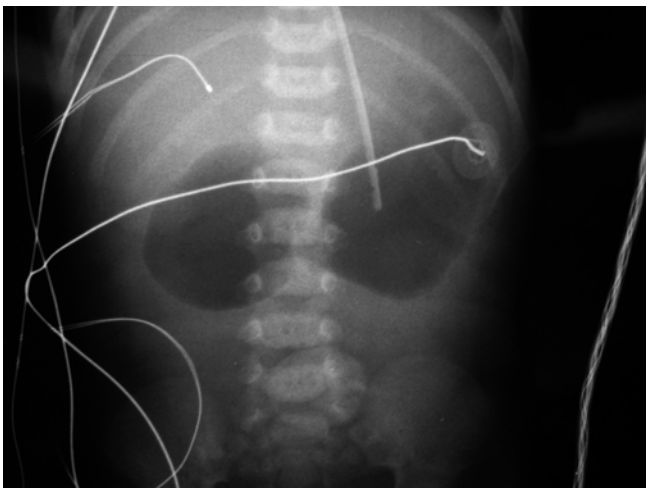

Fig. 9.9 Abdominal radiograph of a term newborn infant revealing a "double bubble" and a lack of distal intestinal gas, consistent with duodenal atresia

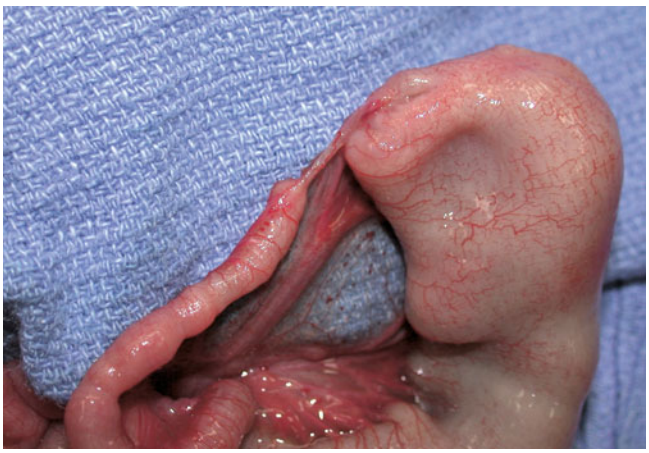

Fig. 9.10 Operative image of a Type II jejunal atresia with a fibrous band separating two atretic ends of the bowel

erect or in the decubitus position is necessary to delineate the duodenal component. If the rare combination of esophageal atresia and duodenal atresia is present, ultrasonography is preferred only to rule out the possibility of midgut volvulus, in which case the mesenteric vessels will be juxtaposed.

If a diagnosis cannot be obtained from the history and plain radiographs, an upper gastrointestinal contrast study can be defining. This should be performed with an orogastric tube placed as distal as possible with low volumes of contrast injected under continuous fluoroscopic surveillance to limit the risk of aspiration. The addition of a contrast enema provides limited support in the evaluation of duodenal atresia. Certainly it may demonstrate a malpositioned cecum but is not always diagnostic of malrotation and volvulus. The finding of a microcolon should increase concern for possible synchronous distal bowel atresia(s) which is encountered in as many as 15 % of patients [86]. Despite the possible advantages of adding a contrast enema, most surgeons can confidently determine the presence of malrotation and additional atresias at the time of operation.

Proximal Obstructions: Jejuno-ileal Atresia

Jejuno-ileal atresias are related to intrauterine vascular accidents including, volvulus, intussusception and congenital bands. Jejuno-ileal atresias are classified according to Grosfeld et al. as Type I: intact bowel with luminal obstruction; Type II: fibrous band separating the two atretic ends (Fig. 9.10); Type IIIa: the two atretic ends separated by a V-shaped mesenteric gap; Type IIIb: the christmas tree deformity with the distal end supplied retrograde by the ileocolic or right colic artery, and Type IV: multiple atresias [87]. The management of jejuno-ileal atresia is usually straightforward. Once diagnosed, infants devoid of significant co-morbidity undergo surgical intervention, often with resection of the atretic segment and anastomosis to restore intestinal continuity. In instances of foreshortened intestine, a proximal tapering enterostomy may preserve bowel length. In infants with more distal atresias associated with peritonitis or meconium cysts, a temporary stoma may be required. Overall survival is 88–90 % but many infants may have associated dysmotility and require temporary parenteral nutrition postoperatively. Up to 10 % of patients with jejuno-ileal atresia may have cystic fibrosis suggesting that all of these babies should have a sweat chloride test and/or genetic testing [88].

Distal Obstructions: Hirschsprung's Disease

Failure to pass meconium in a newborn is a common scenario in neonatal intensive care units. The differential diagnosis should always include anatomic abnormalities (imperforate anus and anal stenosis), meconium plug syndrome, meconium ileus, small left colon and neuromotor disorders most commonly Hirschsprung's disease. Any baby presenting with meconium disease should be evaluated for cystic fibrosis and Hirschsprung's disease. Both may occur in instances of meconium plug syndrome and almost all babies with meconium ileus have cystic fibrosis. The optimal study remains a gastrograffin enema, prior to digital rectal exam since a premature digital exam can alleviate rectal spasm and increase the chance of obtaining a false negative study for Hirschsprung's disease (Fig. 9.11).

If there is radiographic suspicion for Hirschsprung's Disease, the diagnosis should be confirmed by suction rectal biopsy, a relatively simple bedside procedure. Once the diagnosis is confirmed by pathologic absence of ganglion cells in the rectal submucosa, the surgeon will elect one of many possibilities dependant on the infant's condition, extent of involved bowel and the technical experience and capability of the surgical team. Most infants have short segment disease

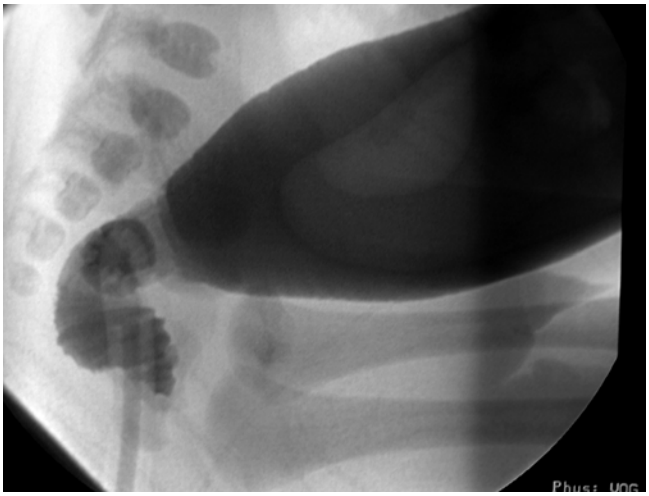

Fig. 9.11 Contrast enema in a term newborn infant revealing a distal transition from dilated to contracted bowel, consistent with Hirschsprung's disease

and are successfully managed with immediate or delayed primary transanal excision of the involved bowel with an anal anastomosis (Soave pull-through procedure). The use of the modified Duhamel procedure and Swenson pull through operations are well recognized and acceptable alternative procedures [89]. The greatest concern for any infant awaiting operation or in the postoperative period is enterocolitis. The onset of enterocolitis can be rapid and quickly fatal if not promptly recognized and treated. The management scheme should include broad spectrum antibiotics including anaerobic coverage (e.g., ampicillin, gentamycin and clindamycin). Equally critical to the management is evacuation of retained gas and stool above the narrowed or diseased segment. This is best accomplished with anal dilations along with insertion of a rectal tube for rectal irrigations. Specifically, a soft catheter (Foley or silastic chest tube; 20–24 French) is gently inserted until resistance is met. Abdominal massage and irrigations with saline (10 mL/kg, repeated 3–4 times) helps alleviate retained stool and flatus. The response is typically characterized by an explosive passage of gas and stool with near immediate relief of abdominal distension for the distressed infant. This routine is usually necessary three times per day initially and can ultimately be performed by the parents once the child is well. Newborn infants who fail this conservative approach may require a temporary colostomy at the most distal site of normally innervated colon. In 10 % of the cases, both the proximal colon and the distal small bowel may be aganglionic (total colonic aganglionosis). In these instances, a temporary stoma may also be required. Hirschsprung's disease, although typically not lethal, requires lifelong attention by the parents and patient to maintain a consistent stooling pattern with social continence. Subclinical dysmotility may manifest itself when affected children are admitted with unrelated diagnoses such as an upper respiratory illness or urinary tract infection. The management of dilations and irrigations remains the mainstay of therapy.

Distal Obstructions: Meconium Plug Syndrome

The most common reason for an infant to not successfully pass meconium in the first few days of life is meconium plug syndrome. This is an entity distinctly separate from meconium ileus (see below). Thick inspissated stool causes a transient obstruction. The newborn will present with generalized abdominal distention, bilious emesis and failure to pass meconium. The contrast enema is diagnostic revealing multiple plugs of stool and is often therapeutic as well.

Distal Obstructions: Meconium Ileus and Meconium Disease of the Preterm Infant

Neonatal intestinal (non-colonic) obstruction due to intraluminal concretions of meconium is referred to as meconium ileus. In contradistinction to infants with meconium plug syndrome, the etiology in meconium ileus is abnormal meconium (mucoviscidosis) resulting from deficient pancreatic and intestinal secretions as well as an abnormal concentration of the meconium within the duodenum and proximal jejunum. In uncomplicated meconium ileus, the neonate may appear relatively normal for the first 12–18 h of life, often tolerating several feeds. As the proximal bowel fills with swallowed air, abdominal distention and emesis ensues, followed by failure to pass meconium. The true obstruction is not often obvious until 24–36 h of life.

The neonate with suspected bowel obstruction should be treated with an orogastric tube to decompress the stomach and intravenous fluids to replace both preexisting fluid deficits and ongoing losses. Antibiotics are administered as the differential diagnosis of a newborn with this presentation includes sepsis. Once again, plain abdominal radiographs and decubitus views usually demonstrate similar sized dilated loops of intestine *without* air-fluid levels. A *soap bubble* appearance is often noted in the right lower quadrant a result of air mixing with the thick meconium. Evidence of distal obstruction should prompt a contrast enema. The enema will demonstrate a microcolon and may also document the presence of meconium pellets in the proximal ascending colon and terminal ileum (Fig. 9.12). In addition, the contrast enema will also exclude cases of colonic atresia, small left colon syndrome and meconium plug syndrome and also document the location of the cecum to rule out anomalies of rotation and fixation. Neonates with distal ileal atresia and total colonic aganglionosis may have a similar appearance of a microcolon on a contrast enema examination, but these

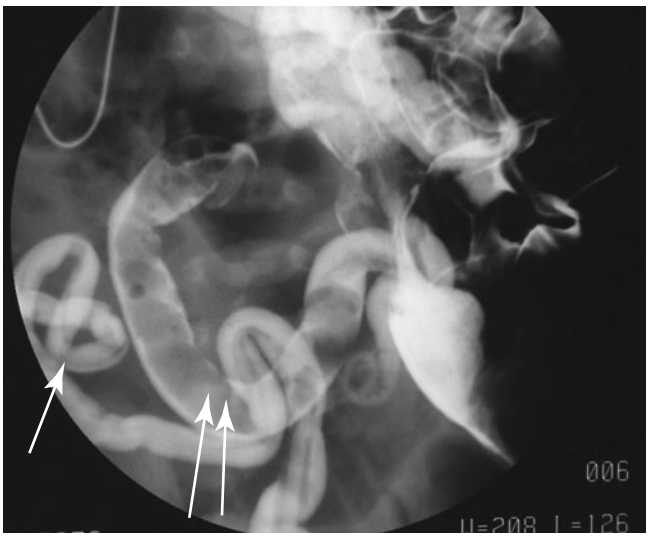

Fig. 9.12 Contrast enema (prone position) of a newborn revealing a microcolon (*single arrow*) and inspissated meconium in the ileum (*double arrow*)

neonates usually have air-fluid levels in the dilated proximal small bowel and absence of pellets in the distal ileum and proximal colon. Non-operative treatment with a hypertonic contrast enema is beneficial due to the hyperosmolar nature of Gastrografin (1,100–1,900 mOsm/l), which also contains a cathartic wetting agent (Tween 80). This draws large volumes of fluid into the bowel lumen, thus washing out the obstructing meconium. The enema is gently administered under fluoroscopic control and the contrast material flushed around the obstructing meconium pellets in the terminal ileum [90]. The Gastrograffin enema is often repeated if necessary. In the author's' experience, this management was successful in resolving the obstruction in approximately 55 % of cases [91]. More recent reports from other institutions have yielded higher success rates. Prior to any contrast studies routine fluid resuscitation is employed with supplemental fluids given in anticipation of increased losses into the gastrointestinal tract following the hypertonic enema. *N*-acetylcysteine (2.5–5 %; 5 ml every 6 h) may be administered by orogastric tube to aid in clearing the thickened meconium from above.

A more complicated course of meconium ileus may occur, typically presenting with distended loops of small bowel with air-fluid levels, intraperitoneal calcifications from antenatal perforation, extravasation of meconium, mass effect (cystic meconium peritonitis) or ascites. If signs of complicated meconium ileus are present or when enema therapy fails to evacuate the obstructing meconium, operative intervention is necessary. Surgical methods to evacuate the meconium and restore intestinal continuity have varied over time [92–98]. Currently for uncomplicated cases that do not respond to gastrograffin enema, we first amputate the tip of the appendix for intestinal irrigation and manual evacuation of obstructing meconium pellets into the colon, avoiding the need for stomas or bowel resection. In cases complicated by intestinal atresia or volvulus, resection and primary anastomosis is preferred. In instances of perforation and those associated with giant cystic meconium peritonitis, a temporary stoma is recommended.

In the postoperative period an evaluation for cystic fibrosis is mandated. Infants must be at least 2 kg and 72 h old to obtain the 100 mg of sweat required. Recently, genetic analysis of a buccal smear is clearly diagnostic in some genetic defects, but more expensive and often takes 2–3 weeks for final results to become available [99–101]. With initiation of feeds pancreatic enzyme therapy should be initiated. Pediatric pulmonary consultation should be obtained to assist in counseling the parents and to optimize maintenance pulmonary therapy since this will be the major cause of morbidity and mortality long term.

A distinctly separate entity of similar origin is meconium disease of prematurity. This disorder is characterized by the development of neonatal meconium obstruction without cystic fibrosis. It occurs exclusively in premature neonates and the typical baby develops obstructive symptoms at 10–14 days of life, often after passing initial meconium [102]. The meconium is inspissated in the terminal ileum and proximal colon and plain radiographs demonstrate bowel distention. In the absence of clinical features of NEC, a water soluble contrast enema should be performed in order to clear the obstruction. If the child fails to respond to the initial enema, additional therapeutic studies may be required. Vinograd and colleagues [103] in a series of seven neonates with this disorder had a 100 % clearance rate with enemas with four of the children requiring more than one enema. Several premature infants at the author's institution have failed non-operative management requiring manual evacuation of the obstructing meconium, occasionally resulting in a temporary ostomy.

Conclusion

A clear understanding of the alterations in basic physiology induced by surgical intervention will influence the quality of care and management of any infant or child following surgery. With congenital or acquired lesions, a thorough understanding of the pathophysiology related to the underlying condition and the corrective operative measures reduces the risk of iatrogenic injury in the perioperative period. Although successful outcome for congenital anomalies and acquired surgical disease relies heavily on operative technique, optimal outcome requires close attention to detail and thoughtful postoperative management by physicians experienced in the surgical care of the neonate and child.

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Perioperative Care of the Pediatric Neurosurgical Patient

10

Monica S. Vavilala and Sulpicio G. Soriano

Abstract

The management of infants and children with conditions of the brain and spinal cord can be challenging, and optimal management requires a thorough understanding of the developmental stages, age related physiological changes, and the pathophysiological processes that occur with these conditions. Patients with neurological conditions often undergo neurosurgical procedures and encounter clinicians from a variety of specialties. The perioperative period, is therefore, an important therapeutic window and clinicians who manage these patients during this period can provide patients with the opportunity to achieve full neurological recovery before, during, and after neurosurgery. For the preoperative period, pediatricians and emergency physicians are able to diagnose urgent/emergent neurosurgical conditions, prepare patients neurosurgery and prevent clinical deterioration from neurological conditions until definitive therapy such as neurosurgery can be provided. During surgery, anesthesiologists aim to provide optimal brain physiological conditions and optimal anesthetic and hemodynamic care during complex neurosurgical procedures. During the postoperative period, intensivists are responsible for anticipating and preventing postoperative consequences, and for helping patients achieve full neurological recovery. This chapter provides information on the neurological issues that should be considered during the perioperative period in the care of children undergoing neurosurgery.

Keywords

Neurosurgery • Brain • Perioperative • Critical care

Abbreviations

ADH	Antidiuretic hormone
ATLS	Advanced Trauma Life Support
ATP	Adenosine triphosphate
AVM	Arteriovenous malformations
BBB	Blood brain barrier
CBF	Cerebral Blood Flow
CBFV	Cerebral blood flow velocity\
cCAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CMR	Cerebral metabolic rate
CMRglu	Cerebral metabolic rate for glucose
$CMRO_2$	Cerebral metabolic rate of oxygen
CNS	Central Nervous System

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CO_2	Carbon dioxide
CO_2R	Reactivity to Carbon dioxide
CPP	Cerebral perfusion pressure
CS	Cortical stimulation
CSF	Cerebro-spinal fluid
CSW	Cerebral salt wasting
CT	Computed tomography
CVR	Cerebrovascular resistance
DI	Diabetes insipidus
ECoG	Electrocorticography
EEG	Electroencephalogram
EMG	Electromyography
ET-1	Endothelin-1
GCS	Glasgow Coma Scale
HR	Hoffman reflex
ICP	Intracranial Pressure
ICPm	Intracranial Pressure monitoring
IHAST	International Hypothermia in Aneurysm Surgery Trial \
IM	Intramuscular
iTBI	Involving Traumatic Brain Injury
IV	Intravenous
LLA	Lower Limit of Autoregulation
MAC	Minimum alveolar concentration
MAP	Mean Arterial Pressure
MEP	Motor evoked potentials
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
NIRS	Near infrared spectroscopy
NO	Nitric oxide
NOS	Nitric oxide synthase
O_2	Oxygen
$PaCO_2$	Partial pressure of arterial carbon dioxide
PALS	Pediatric Advanced Life Support
PaO_2	Partial pressure of oxygen in arterial blood
PG	Prostaglandin
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SBP	Systolic blood pressure
SCI	Spinal cord injury
SCIWORA	Spinal cord injury without radiological abnormalities
SDR	Selective dorsal rhizotomy
$SjvO_2$	Jugular venous oxygen saturation
SSEP	Somatosensory evoked potentials
TBI	Traumatic Brain Injury
TCD	Transcranial Doppler
TIVA	Total intravenous anesthesia
VAE	Venous air embolus (or emboli)
V_{BAS}	Basilar artery flow velocity
V_{MCA}	Middle cerebral artery flow velocity

Introduction

The perioperative management of pediatric neurosurgical patients presents challenges to physicians from many disciplines including pediatricians, emergency medicine physicians, neurosurgeons, anesthesiologists, and intensivists. A basic understanding of age-dependent variables and the interaction between preoperative, anesthetic, and surgical conditions and needs are essential to minimizing perioperative morbidity and mortality and to optimizing outcomes after neurosurgery. This chapter will highlight these age-dependent physiological and pathophysiological changes relevant to the perioperative (preoperative, intraoperative and postoperative) management of the pediatric neurosurgical patient.

Developmental Physiology of the Nervous System

Intracranial Pressure (ICP)

Under normal physiological conditions, ICP is 2–6 mmHg in full term infants and higher in children and adults (0–15 mmHg). Intracranial compliance is defined as the change in intracranial pressure relative to the intracranial volume. As intracranial volume acutely rises, the ability to compensate due to lack of compliance reduces and ICP increases. Acute increases in cranial volume due to massive hemorrhage or obstructed cerebro-spinal fluid (CSF) flow cannot be attenuated by expansion of the cranial vault and frequently result in life-threatening intracranial hypertension in infants [1]. Once the fontanelles and sutures have closed, children have a relatively smaller cranial volume and lower intracranial compliance than adults. Contributory factors to increases in ICP include a higher ratio of brain water content, less CSF volume, and a higher ratio of brain content to intracranial capacity [2]. Intracranial hemorrhage, inflammation/infection, tumors or congenital malformations can lead to decreased CSF absorption with possible elevations in ICP. Pediatric neurosurgical patients may have elevated ICP during the perioperative period due to any of these processes described above from preoperative or post surgical hemorrhage of any space occupying lesion.

Cerebral Blood Flow (CBF)

Complex homeostatic mechanisms regulate the cerebral circulation during the perioperative period and these must be considered when managing systemic and cerebral hemodynamics. Factors influencing CBF are: (1) cerebral

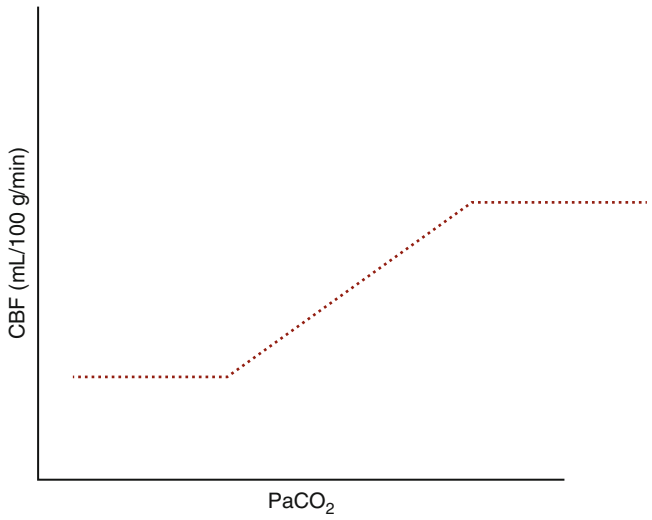

Fig. 10.1 Relationship between $PaCO_2$ and cerebral blood flow

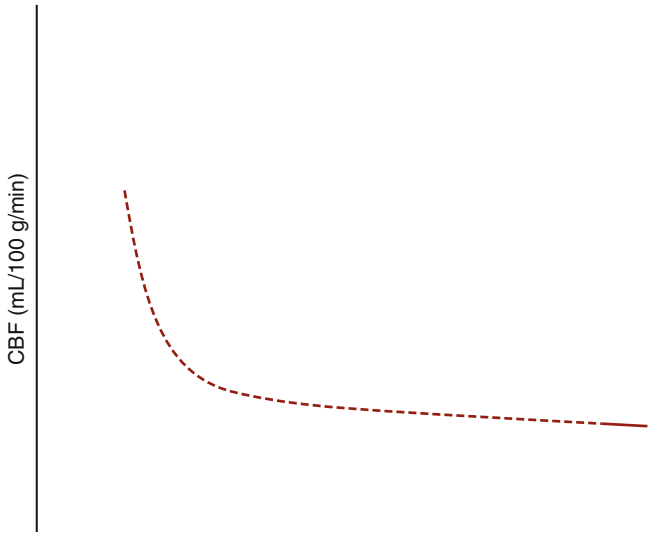

Fig. 10.2 Relationship between PaO_2 and cerebral blood flow

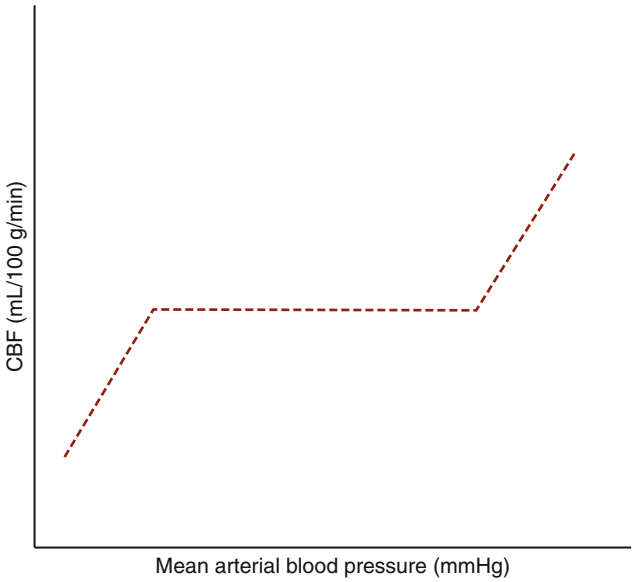

Fig. 10.3 Relationship between mean arterial pressure and cerebral blood flow (normal cerebral autoregulation)

metabolism, (2) partial pressure of arterial carbon dioxide ($PaCO_2$) (Fig. 10.1) (3) partial pressure of oxygen in arterial blood (PaO_2) (Fig. 10.2) (4) blood viscosity and (5) cerebral autoregulation (Fig. 10.3). Flow-metabolism coupling is the most significant regulator of the cerebral circulation and is typically preserved [3–5]. However, during periods of central nervous system (CNS) activation, CBF increases more than $CMRO_2$, resulting in a decrease in the cerebral oxygen extraction fraction [6] During development, CBF changes with age, mirroring changes in neural development and synaptogenesis. The healthy brain receives about 15 % of cardiac output and normal adult CBF is approximately 50 mL/100 g/min. There are relatively few data on CBF available from healthy children. In one older study, Kennedy and Sokoloff found CBF to be much higher, on the order of 100 mL/100 g/min, in conscious healthy children [7]. A recent study using arterial spin labeling found similar values in young children [8], which then decrease and approach adult values during the adolescent years, suggesting that CBF increases during early childhood, peaks during early-mid childhood and plateaus during late childhood at approximately 7–8 years [9].

Compared to $PaCO_2$, the influence of PaO_2 on the cerebral circulation is of much less clinical significance. There are minimal changes in CBF with changes in PaO_2 above 50 mmHg below a threshold of PaO_2 of 50 mmHg, CBF increases to maintain adequate cerebral oxygen delivery. Cerebral blood flow may be excessive (hyperemia) or inadequate (ischemia) relative to cerebral metabolism during the perioperative period, these changes may be focal, regional and or global, and advanced neuromonitoring techniques may aid in increasing our understanding of the pathophysiological processes involved.

Cerebral Metabolic Rate (CMR)

Global CMR for oxygen and glucose is generally higher in children than in adults (oxygen 5.8 vs. 3.5 mL/100 g brain tissue/min and glucose 6.8 vs. 5.5 mL/100 g brain tissue/min respectively [7]). Similar to age related changes in CBF, studies of healthy anesthetized children also suggest age-related increases in $CMRO_2$, which are 104 μmol/100 g/min in infants and 135 μmol/100 g/min in children ages 3 weeks–14 years [8]. Similar to $CMRO_2$, cerebral metabolic rate for

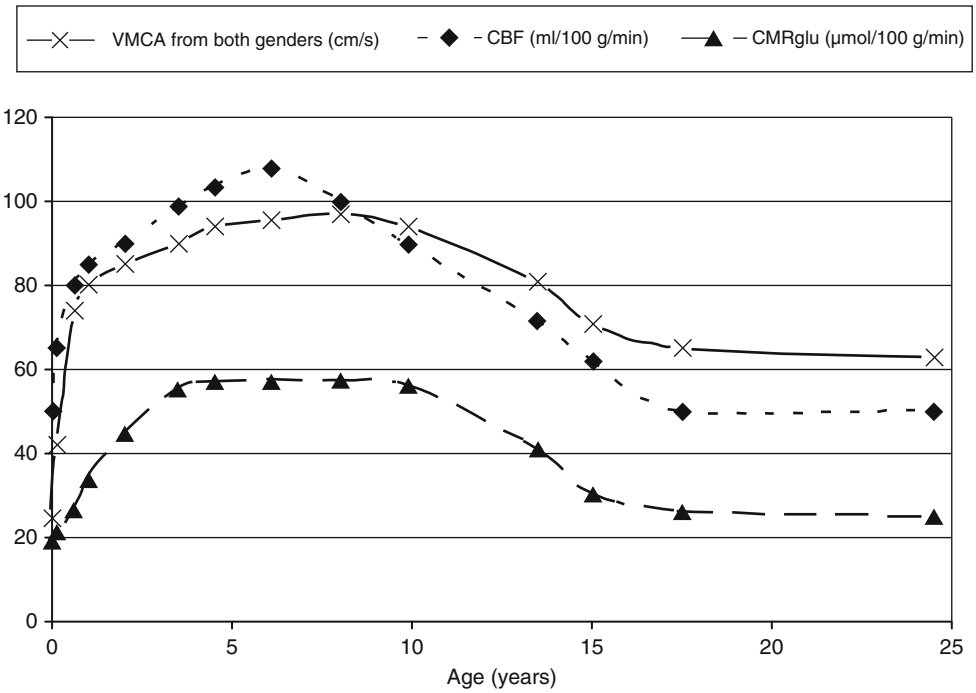

Fig. 10.4 Age-related changes in mean flow Velocity of Middle Cerebral Artery (*VMCA*) in both sexes, Cerebral Blood Flow (*CBF*), and Cerebral Metabolic Rate of Glucose (*CMRglu*). Corresponding Adult Values: VMCA 50 cm/s, CBF 50 mL/100 g/min, CMRglu 19–33 mol/100 g/min

glucose (CMRglu) is lower at birth (13–25 µmol/100 g/min), increases during childhood, peaks by 3–4 years (49–65 µmol/100 g/min), and remains high until 9 years of age. Thereafter CMRglu decreases, and approaches adult rates (19–33 µmol/100 g/min) [10]; changes in $CRMO_2$ and CRMGlu mirror age-related changes in CBF (Fig. 10.4). Cerebral metabolic rate of oxygen and glucose may be altered in children with neurosurgical conditions during the perioperative period, especially while receiving sedation, and or while recovering from general anesthesia.

CO_2 Reactivity

$PaCO_2$ is the most powerful modulator of the cerebral circulation and the cerebral circulation is exquisitely sensitive to changes in $PaCO_2$ [11, 12]. Yet, much of our therapy aimed to modulate changes in CBF via changes in $PaCO_2$ is empiric, and without knowledge of individual patients CO_2 reactivity or CBF response to the intervention made. Similar to CBF and metabolism, carbon dioxide (CO_2) reactivity may be higher in healthy children than in adults [13–15]. Studies suggest that reactivity to CO_2 is well developed even in healthy preterm infants [16] and that CO_2 reactivity in newborns correlates with the lowest pH and may reflect the severity of perinatal asphyxia [17]. One recent study suggests that CO_2 reactivity and cerebral autoregulation may be altered in patients undergoing tumor resections (Fig. 10.5). While these data are from adults, it is possible that the same pathophysiological processes occur in children.

Viscosity and CBF

Compared to $PaCO_2$, the influence of viscosity on the cerebral circulation is less. There are minimal changes in CBF with changes in PaO_2 above 50 mmHg below a threshold of PaO_2 of 50 mmHg, CBF increases to maintain adequate cerebral oxygen delivery. Unlike CO_2R, the equilibration of CBF is longer and takes approximately 6 min after the establishment of hypoxemia [18]. The influence of oxygen, on the cerebral circulation is less so than exerted by $PaCO_2$. Variability in Hct in children undergoing neurosurgery may lead to variability in CBF, CBV and ICP.

Cerebral Autoregulation

Cerebral autoregulation is an important homeostatfic regulator of CBF where arterioles dilate and constrict to maintain CBF nearly constant over a range of blood pressures. In healthy adults, changes in mean arterial pressure (MAP) between 60 and 160 mmHg results in little or no change in CBF [19, 20]. This adaptive mechanism maintains constant (adequate) CBF by vasodilation or decreasing cerebrovascular resistance. Under normal conditions, beyond these limits of autoregulation, hypotension may result in cerebral ischemia, and hypertension may cause cerebral hyperemia.

Healthy infants appear to autoregulate CBF as well as older children, but the long held assumption that the lower limit of autoregulation (LLA) is lower in younger compared to older children may not be valid (same LLA range for

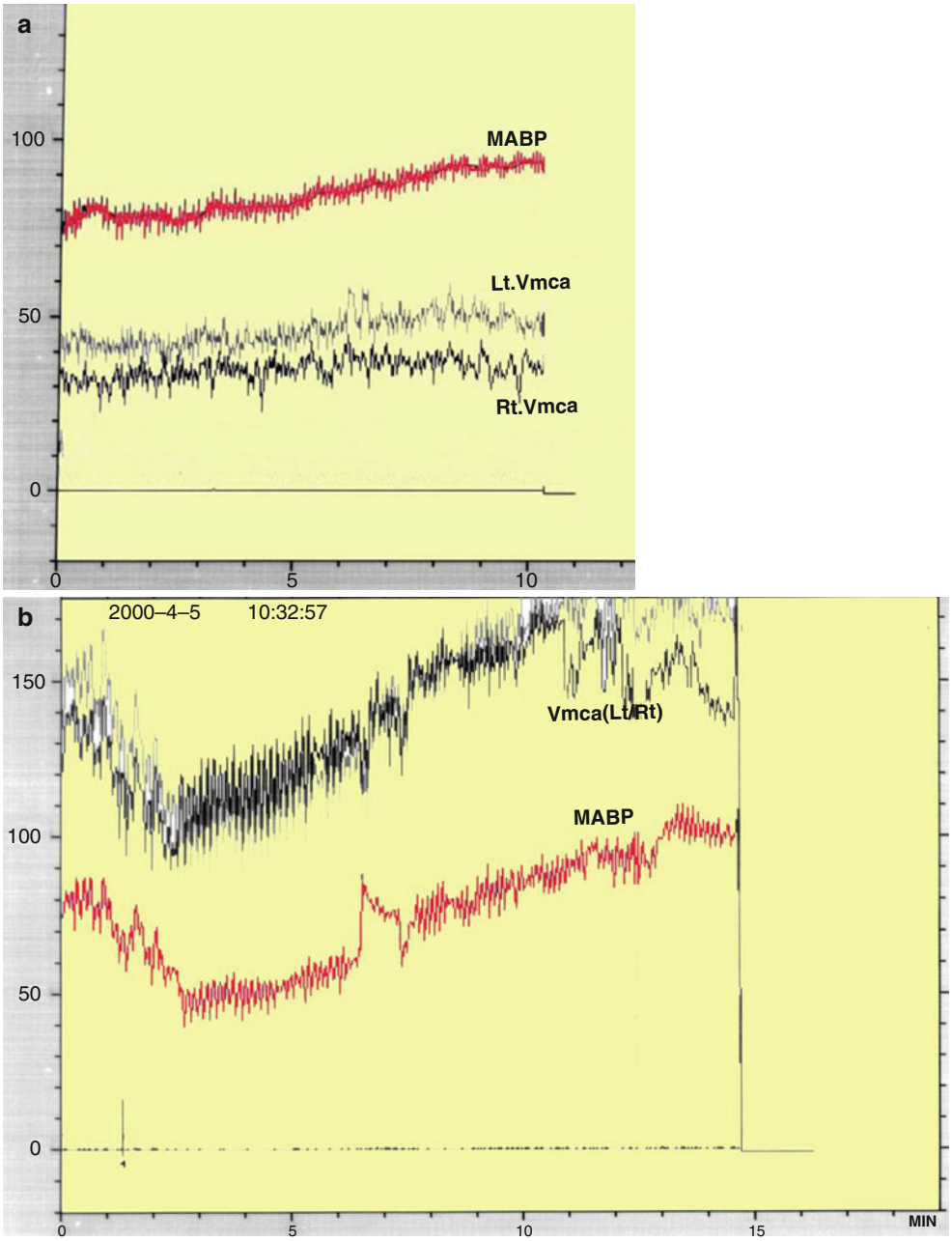

Fig. 10.5 Intact (**a**) and impaired (**b**) Cerebral autoregulation

younger and older children 46–76 mmHg) [21]. There are no data on the LLA in healthy neonates. However, estimates of the lower limit of autoregulation derived from the cerebral oximetry index in pediatric patients undergoing cardiopulmonary bypass were at 42 ± 7 mmHg [22]. Since blood pressure increases with age, neonates and young children may be at increased risk of cerebral ischemia due to lower blood pressure reserve (mean arterial pressure – LLA) and narrow autoregulatory range [23] and during critical illness, CBF may be completely pressure passive [24]. Therefore, tight blood pressure control is essential in the management of neonates to minimize both cerebral ischemia during hypotension and intraventricular hemorrhage with increased blood pressure. There may also be age-related differences in the time to return of normal autoregulation in young children [25] but there are no data on this in neonates. Animal data suggest that while CBF pressure autoregulation and reactivity to CO_2 operate in the newborn rat, hypercapnia abolishes cerebral autoregulation [23] and that abolished autoregulation is associated with cerebral damage in asphyxiated infants. Moreover, the combination of isoelectric electroencephalograms and cerebral hyperperfusion is an early indicator of very severe brain damage [16]. Despite these clinical observations, mechanisms of normal cerebral autoregulation in healthy children and adaptations in acute disease are not completely understood and like changes in CBF, both

anatomic and physiological maturation might play a role in the development of a fully developed autoregulatory response. Children with neurosurgical conditions such as traumatic brain injury (TBI) or tumors may have impaired cerebral autoregulation during the peri-operative period, requiring clinicians to actively provide tight control of systemic and cerebral hemodynamics [26].

Pharmacology of the Nervous System

Intravenous sedative and anesthetic drugs affect cerebral hemodynamics and have varying cerebral hemodynamic profiles. Different classes of sedatives differentially impact cerebrovascular resistance, cerebral autoregulation, CBF, and CMR. Preoperative sedation and analgesia choice may impact intraoperative cerebral hemodynamics, and intraoperative use of volatile anesthetic agents may affect post operative recovery and outcomes. Post operative choice of sedation and analgesia may influence the clinician's ability to perform an adequate neurological examination and prevent timely tracheal extubation.

Propofol

It has been reported that propofol maintains cerebral autoregulation and cerebrovascular reactivity to carbon dioxide above 30 mmHg end-tidal carbon dioxide levels in children [27]. Furthermore, propofol, at high doses, lowers CBF and mean arterial pressure values in children, which may be mediated by its cerebral vasoconstrictive properties [28]. Propofol may depress systemic blood pressure but both potently decrease $CMRO_2$, CBF, and ICP [29]. Propofol has been purported to have neuroprotective properties, especially in preclinical studies, but its clinical efficacy in neurologically compromised pediatric patients has not been tested. Etomidate and ketamine are less likely to cause hypotension than propofol. However, CNS excitation and increased ICP have been associated with these drugs respectively, and they may not be appropriate for many neurosurgical patients. Finally, propofol infusion syndrome which characterized by the lactic acidosis, rhabdomyolysis, and circulatory collapse after prolonged administration of propofol, in children, precludes its use for sedation beyond 48 h in the PICU setting [30].

Barbiturates

Barbiturates decrease CBF, CBV, and $CMRO_2$ in a dose dependent manner [31–33] and therefore reduce ICP. Neither CBF nor cerebral metabolism is significantly altered by subanesthetic doses of barbiturates. When the electroencephalogram (EEG) becomes isoelectric, CBF and $CMRO_2$ decrease to about 50 % of normal, and additional doses of barbiturates have little further effect. Barbiturates may also be used to prevent increases in ICP that can occur with laryngoscopy and tracheal intubation. Autoregulation and the cerebrovascular response to changes in $PaCO_2$ remain intact during barbiturate anesthesia. The rate of CSF formation and the resistance to reabsorption of CSF are not altered by barbiturates [34]. In doses that suppress the EEG, barbiturates reduce cerebral damage in animal and human models of focal cerebral ischemia [35, 36]. In animals, barbiturates also reduce the extent of cerebral edema after a cortical freeze injury. This decrease in edema is in contrast to the response observed with the volatile anesthetics [37].

Opioids

Opioids are commonly used as a part of a sedation plan during the perioperative period in neurosurgical patients. In general, opioids have little effect on CBF, CBV, or ICP unless respiration is depressed and $PaCO_2$ is increased [38–41]. Fentanyl, for example, is generally considered safe in pediatric neurosurgical patients and does not alter the rate of CSF formation, though it does reduce the resistance to CSF reabsorption by 50 % [42, 43]. The neonatal cerebral circulation is unaffected by fentanyl [44]. At conventional doses, sufentanil [45, 46] and alfentanil [47] do not appear to have adverse effects on the cerebral vasculature or upon ICP in most patients. In a subset of patients with severe head injuries and very poor intracranial compliance, sufentanil may cause a small (e.g., 10 mmHg) and transient increase in ICP that may be clinically significant in some settings [48–50]. Remifentanil is an ultra–short-acting opioid that is rapidly metabolized by plasma cholinesterases and has gained in popularity for use as part of the general anesthetic technique. The very short clinical duration of effect of remifentanil and its context-sensitive half life that is independent of the duration of infusion [51, 52] make it an appealing opioid for lengthy neurosurgical procedures, after which rapid return of consciousness is desirable. As is the case with other opioids that have been studied, remifentanil does not increase CBF or ICP [53, 54]. Remifentanil, like other opioids, preserves cerebral autoregulation and CO_2 reactivity [55–58]. Return of consciousness is very rapid after remifentanil is discontinued, and the frequency of administration of naloxone to permit neurologic assessment is decreased [59]. However, because remifentanil analgesia is very brief after its discontinuation, a long-acting opioid analgesic must be administered to prevent severe pain and rebound hypertension before or soon after remifentanil is discontinued [60, 61].

Etomidate

Etomidate reduces ICP by decreasing CBF and $CMRO_2$ by 34 and 45 %, respectively. It, too, preserves the CO_2 responsiveness of the cerebral circulation [62, 63]. A side effect of etomidate administration is myoclonus. Myoclonus has been reported after prolonged continuous infusion of etomidate [64].

Lidocaine

Lidocaine in clinical doses decreases CBF and reduces the increase in ICP associated with endotracheal intubation [65, 66]. The *benzodiazepines* (diazepam, lorazepam, and midazolam) decrease CBF and $CMRO_2$ approximately 25 % [67–72]. Adrenal suppression remains a concern.

Ketamine

In contrast to the other intravenous anesthetic agents, ketamine is a potent cerebrovasodilator. Ketamine increases CBF by 60 % with little change in $CMRO_2$ [73–75]. The cerebrovascular response to administration of ketamine is thought to be the result of regional cerebral activation induced by the drug [76]. Ketamine produces a marked increase in ICP, which can be reduced, but not prevented, by hyperventilation [74, 77, 78]. The increase in CBF, and presumably in ICP, can be blocked by previous administration of thiopental [73]. Ketamine has been associated with sudden elevation of ICP and clinical deterioration when used in patients with hydrocephalus and other intracranial pathology [78–80]. While ketamine is currently not routinely used as a general anesthetic in patients with reduced intracranial compliance, one recent study in critically ill children reported decreases in ICP following ketamine [81], thereby questioning the notion that ketamine increases ICP.

Dexmedetomidine

Dexmedetomidine is a selective alpha 2 agonist sedative hypnotic agent with a short half life that reduces sympathetic tone and is associated with decreasing opioid needs, benzodiazepines, propofol, and other sedative medication needs. Short-term sedation has been shown to be safe in studies, although hypotension and bradycardia are the most significant side effects with rebound hypertension occurring after abrupt cessation [82–86]. These side effects can be ameliorated by a low dose infusion without bolus (generally $\leq$0.5 μg/kg/h). In adults, dexmedetomidine decreases CBF in a dose related manner, decreases CMR, and preserves flow metabolism coupling, though it may decrease dynamic autoregulation [87, 88]. One small series found no adverse effect on brain PbO_2 with dexmedetomidine. Dexmedetomidine has been used as a sedative to facilitate awake craniotomy [89]. Overall, dexmedetomidine is emerging as an effective therapeutic agent in the management with a favorable cerebrovascular profile [90].

Neuromuscular Blocking Agents

Succinylcholine is a depolarizing neuromuscular blocking agent and is associated with life-threatening hyperkalemia and cardiac arrest in children with undiagnosed myopathies and has a U.S. Food and Drug Administration "black box warning". Life-threatening hyperkalemia has been associated with succinylcholine administration in many types of central nervous system disorders, including TBI [90–93], near-drowning [94] subarachnoid hemorrhage [95], encephalitis [96], cerebrovascular accidents [97], and paraplegia [98, 99]. The onset of the period of vulnerability may begin as early as 24–48 h after injury and may last up to 1–2 years after injury [98]. Because the period of risk for succinylcholine-induced hyperkalemia after cerebral injury is undefined, succinylcholine should be avoided in these patients, except in the period immediately after injury. Succinylcholine can increase CBF and ICP in patients with reduced intracranial compliance [100–103] probably because of cerebral stimulation from succinylcholine-induced increases in afferent muscle spindle activity [104]. In contrast, most nondepolarizing relaxants have little effect on CBV and ICP [105–108] unless associated with histamine release (*d*-tubocurarine, atracurium), which causes transient cerebrovasodilation and increased ICP [109]. Succinylcholine use in critically ill children, especially in those who have not been ambulatory for 48 h is not recommended. Hemiplegia from an upper motor neuron lesion (such as a stroke or a brain tumor) is associated with resistance to nondepolarizing relaxants on the paretic side [110–112] Excessive doses of muscle relaxants may be given if dosage is guided by a nerve stimulator monitoring a hemiplegic extremity. In contrast, an increased response to nondepolarizing muscle relaxants is observed in paretic muscle lower motor neuron lesions (e.g., paraplegia and quadriplegia) [113]. Acute administration of several anticonvulsants, including phenytoin and phenobarbital, enhances nondepolarizing neuromuscular blockade or delays its reversal [114, 115]. Importantly, many patients who have been receiving chronic phenytoin or carbamazepine therapy are relatively resistant to the effects of nondepolarizing relaxants [116–119], including rocuronium [115, 120], due to enhanced metabolism [121, 122].

Cerebral Vasodilators

Direct-acting vasodilators, including sodium nitroprusside, adenosine, nitroglycerin, diazoxide, and hydralazine, which may be used intraoperatively and into the postoperative period, impact cerebral physiology. These agents are cerebrovasodilators and may increase CBF and ICP [123–126]. The calcium channel blockers also raise CBF and ICP [127, 128]. These drugs should therefore be avoided in patients with reduced intracranial compliance, unless the dura is open or ICP is being monitored. Sodium nitroprusside lowers the range of cerebral autoregulation. Brain-surface oxygen tension is greater [129] and metabolic disturbances in brain biochemistry (e.g., lactate, pyruvate, and phosphocreatine levels) are less during nitroprusside-induced hypotension than with trimethaphan-induced or hemorrhage-induced hypotension [130].

Fluids, Blood Products, and Electrolytes

Meticulous fluid management is critical in the care of neurosurgical patients in children. Small patient size and immature renal function result in fluid and electrolyte imbalances. Water freely diffuses through the blood brain barrier and disruptions in tight junctions, and inequality of pressure gradients in osmolality, hydrostatic pressure, and colloid oncotic pressure facilitate the net movement of fluid across the blood brain barrier into the brain, resulting in increased ICP. Osmolar gradients are maintained only when the blood brain barrier is intact, otherwise large molecules that are typically excluded such as albumin enter the brain and can worsen edema.

There is no definitive formula for volume replacement for the pediatric neurosurgical patient. Hemodynamic stability during the perioperative period requires careful maintenance of intravascular volume where pre-operative fluid restriction and/or diuretic therapy may lead to blood pressure instability and even cardiovascular collapse if sudden blood loss occurs during surgery. Therefore, normovolemia should be maintained throughout the perioperative period. Estimation of the patient's blood volume is essential in determining the amount of allowable blood loss and when to transfuse blood.

Isotonic crystalloid solutions (Plasmalyte) are commonly used during general anesthetic and for cerebral resuscitation. Rapid infusion of large quantities of normal saline (>60 mL/kg) can be associated with hyperchloremic acidosis [131]. The calculated maintenance rate of fluid administration depends on the weight of the patient [132]. These rates are based on normal physiologic conditions. Increases in insensible losses, blood loss, or other conditions such as diabetes insipidus or the syndrome of inappropriate anti-diuretic hormone excretion, as noted below should be considered when determining the proper amount of fluid administration. Depending on the extent and length of the surgical procedure and exposure of vascular beds, additional fluid administration 3–10 mL/kg/h may be necessary during the intraoperative period. Unlike adults, children can become hypovolemic from scalp injuries and isolated TBI. Hypotonic crystalloids should be avoided during the perioperative period. The role of colloids is controversial. In 2007, the SAFE study reported that adult patients with TBI who received fluid resuscitation with albumin had higher mortality rates compared to those who received fluids with crystalloids [133]. The use of hydroxyethyl starch is discouraged during the perioperative period for resuscitation because of its role in exacerbating coagulopathy. Hypertonic saline 0.1–1.0 mL/kg may be used to increase CPP, but in this setting, studies show that there is no advantage to hypertonic saline compared to conventional pre-hospital fluid protocols [134].

Since the potential for significant blood loss is likely in most craniotomies in infants and children, the maximum allowable blood loss should be determined in advance and a type and cross should be available prior to surgery and during the postoperative period. There are no guidelines regarding an appropriate threshold for transfusing blood in the neurosurgical patient since it is unclear what hematocrit is needed for optimum oxygen delivery for the pediatric brain and in different disease states. Thus, the decision to transfuse should be dictated by the type of surgery, underlying medical condition of the patient, and potential for additional blood loss both intra- and postoperatively. In general, hematocrits of 17–25 % may warrant blood transfusion. Packed red blood cells (10 mL/kg) will raise the hematocrit by 10 %. Blood losses during surgery may be replaced with 3 mL of normal saline for 1 mL of estimated blood loss or a colloid solution such as 5 % albumin of an equal volume to the blood loss. It can be difficult to accurately estimate blood loss during intracranial procedures as the anesthesiologist may have a compromised view of the surgical field as well as having "hidden" blood loss in the drapes or elsewhere.

Infants are at particular risk for perioperative hypoglycemia. Small premature neonates, with limited reserves of glycogen and limited gluconeogenesis, require continuous infusions of glucose at 5–6 mg/kg/min in order to maintain serum levels. At the same time, the stress of critical illness and resulting insulin resistance can produce hyperglycemia that, in turn, is associated with neurologic injury [135, 136] and poor outcomes in adults [137]. However, it is unclear if tight glycemic control offers significant benefits to children [138, 139]. Limited evidence now suggests that tight control may carry undue risk of hypoglycemia and newer data are less supportive of very tight glycemic control [140]. Retrospective studies from children suggest that both hyperglycemia (glucose 200–250 mg/100 mL) and hypoglycemia occur after TBI [141] and that hyperglycemia is associated with poor outcome.

Cerebral edema can be occur during the perioperative period and may result in devastating consequences. Aggressive hyperventilation should be reserved for situations where herniation is impending and immediate life-saving maneuvers are required and data from patients with TBI suggest that even mild hyperventilation leads to hypoperfusion [142]. Elevation of the head above the heart and the use of hyperosmolar therapy (i.e., mannitol/hypertonic saline) are also methods to reduce ICP. Mannitol may be used in doses of 0.25–0.5 g/kg intravenously. This will transiently alter cerebral hemodynamics and raise serum osmolality by 10–20 mOsm/kg [143]. However, repeated dosing can lead to extreme hyperosmolality, renal failure and further brain edema. Hypertonic saline increases serum sodium, decreases ICP and increases CPP titrated to a serum sodium rate change and brain edema [144]. Standard administration at our institution is typically 3 mL/kg as a 3 % via a central line (to avoid phlebitis and tissue necrosis) targeted to a serum sodium rate change of 0.05 meq/h with endpoints depending on initial serum sodium and degree of brain edema (typically 155–160 meq/L). Hypertonic saline concentrations of 2 % may be administrated peripherally. Theoretical risks include central pontine myelinolysis and renal failure. Furosemide is a useful adjunct to mannitol, can reduce CSF formation, and decrease acute cerebral edema as well as preventing rebound swelling due to mannitol [145, 146].

Electrolyte Disorders

Non-osmotic secretion of antidiuretic hormone (ADH) makes hyponatremia common after neurosurgery. Elevated ADH levels can result from a variety of stimuli ranging from pain and nausea to fluid shifts and intravascular hypovolemia. Acute hyponatremia can provoke seizures and may be treated with hypertonic saline, fluid restriction, and administration of diuretics [147]. Cerebral salt wasting (CSW) occurs in approximately 11.3/1,000 procedures [148] with a duration of 6 days [149] in children and can be seen following TBI and other neurosurgical procedures and disease states such as meningitis [150], calvarial remodeling [151, 152], tumor resection [149], and even hydrocephalus [153]. Cerebral salt wasting, the result of excessively high atrial or brain natriuretic peptide levels [154], is marked by hyponatremia, hypovolemia, and excessive urinary excretion of sodium. Although the classic treatment involves saline administration, more rapid resolution has been achieved with fludocortisone [155].

Diabetes insipidus (DI) is a well-known complication of neurosurgical procedures involving or adjacent to the pituitary and hypothalamus, in association with craniopharyngioma, where it can be a presenting symptom in 40 % of cases. Diabetes insipidus is recognized by a rising serum sodium (>145 mg/dL) accompanied by copious (>4 mL/kg/h) output of dilute urine. Severe dehydration and hypovolemia may develop. One effective protocol employs maximal antidiuresis with intravenous vasopressin and strict limitation of intravenous fluids [156]. This strategy avoids the pitfalls of titrating drug to urine output and recognizes that renal blood flow remains normal in the normovolemic, but maximally antidiurese, child. Since urine output can be minimal (0.5 mL/kg/min), other clinical markers of volume status must be assessed.

Preoperative Evaluation and Preparation

Given the urgent nature of many pediatric neurosurgical procedures, a thorough preoperative evaluation may be difficult. However, it is important to obtain a relevant patient history which can reveal conditions that may increase the risk of adverse reactions to anesthesia and perioperative morbidity and identify patients who need more extensive evaluation or whose medical condition needs to be optimized before surgery. The chronicity and severity of the patient's neurological condition will vary greatly and should dictate perioperative management. Special attention should be given to symptoms of allergy to latex products (e.g., meningomyeloceles) [157]. Severe dehydration and electrolyte abnormalities can be the result of protracted vomiting from intracranial hypertension. Patients with diabetes insipidus can develop hypovolemia due to polyuria. During the perioperative period, steroids are frequently initiated to palliate cerebral swelling in patients with intracranial tumors and therapeutic levels of anticonvulsants should be verified preoperatively and maintained. Patients on long-term anticonvulsants may develop toxicity, especially if seizures are difficult to control. This reaction frequently manifests with abnormalities in either the hematologic, hepatic function, or both.

Physical Examination

The preoperative physical examination should, at a minimum, include a brief but serial neurologic evaluation, that includes; (1) level of consciousness, (2) motor and sensory function, (3) normal and pathologic reflexes, (4) integrity of the cranial nerves, and (5) signs and symptoms of intracranial hypertension. Preoperative diagnoses predispose patients to complications such as those listed in Table 10.1. The modified Glasgow Coma Scale for infants and children is useful for assessing the mental status of the patient (Table 10.2). Lesions of the brainstem can manifest with cranial nerve dysfunction such as respiratory distress, impaired gag and swallowing, and pulmonary aspiration. Evidence of muscle atrophy and weakness should be noted, particularly if the

patient is hemiparetic, hemiplegic or bedridden, since up-regulation of acetylcholine receptors may precipitate sudden hyperkalemia following succinylcholine administration and induce resistance to nondepolarizing muscle relaxants in the affected limbs. Body weight should be accurately measured to guide the administration of drugs, fluids, and blood products. Physical signs of dehydration should be noted, especially in patients who have been chronically ill or received osmotic or diuretic agents.

Table 10.1 Perioperative clinical implications for infants and children with neurological conditions

Condition	Clinical implications
Denervation injuries	Hyperkalemia after succinylcholine,
	Resistance to non-depolarizing muscle relaxants, abnormal response to nerve stimulation
Chronic anticonvulsant therapy	Hepatic and hematological abnormalities
	Increased metabolism of anesthetic and sedative agents
Arteriovenous malformation	Potential congestive heart failure
	Seizures
	Increased intracranial pressure
Neuromuscular disease	Malignant hyperthermia
	Respiratory failure
	Sudden cardiac death
Chiari malformation	Apnea
	Aspiration pneumonia
	Stridor
Hypothalamic/pituitary lesions	Diabetes insipidus/SIADH
	Hypothyroidism/hyperthyroidism
	Adrenal insufficiency/adrenal excess

Radiologic and Laboratory Evaluation

Most neurosurgical patients will have a brain magnetic resonance imaging (MRI) or CT scan as part of the preoperative assessment regardless of whether the preoperative period includes the emergency department or the ICU. These scans should be reviewed with the neurosurgeon in order to confirm the primary lesion and the presence of evolving neurological conditions (hydrocephalus, compressed cisterns, and midline shifts). For elective patients undergoing neurosurgery and who otherwise have no reason to have anemia, coagulopathy or electrolyte disturbances, no preoperative laboratory data may be required, as blood samples can be frequently obtained after induction of general anesthesia. In emergent cases, critically ill children, and trauma, the risk of significant blood loss associated with neurosurgery makes it desirable to have a preoperative hematocrit, electrolytes, and coagulation studies (e.g., prothrombin time and partial thromboplastin time). Patients with suprasellar pathology who undergo elective or semi-elective neurosurgery should have a preoperative endocrinology evaluation for ensuring optimized endocrine status (i.e., thyroid function). Type and cross matched blood should be order prior to all craniotomies and this may be facilitated either preoperatively or immediately after induction of anesthesia depending on local blood availability.

Premedication

Patients are typically admitted to the operating room for neurosurgery from the emergency department or ICU. Perioperative anxiety plays a significant role in the care of the pediatric neurosurgical patient for patients, providers and

Table 10.2 Modification of the Glasgow Coma Scale Score for young children

Glasgow Coma Scale	Pediatric Coma Scale	Infant Coma Scale	Score
Eyes	*Eyes*	*Eyes*	
Open spontaneously	Open spontaneously	Open spontaneously	4
Verbal command	React to speech	React to speech	3
Pain	React to pain	React to pain	2
No response	No response	No response	1
Best verbal response	*Best verbal response*	*Best verbal response*	
Oriented and converses	Smiles, oriented, interacts	Coos, babbles, interacts	5
Disoriented and converses	Interacts inappropriately	Irritable	4
Inappropriate words	Moaning	Cries to pain	3
Incomprehensible sounds	Irritable, inconsolable	Moans to pain	2
No response	No response	No Response	1
Best motor response	*Best motor response*	*Best motor response*	
Obeys verbal command	Spontaneous or obeys verbal command	Normal spontaneous movements	6
Localizes pain	Localizes pain	Withdraws to touch	5
Withdraws to pain	Withdraws to pain	Withdraws to pain	4
Abnormal flexion	Abnormal flexion	Abnormal flexion	3
Extension posturing	Extension posturing	Extension posturing	2
No response	No response	No response	1

parents, often related to the cognitive development and age of the child. Preoperative sedatives given prior to the induction of anesthesia can ease the transition from the preoperative holding or ICU area to the operating room [158]. Sedatives are administered in the parents' presence to facilitate a smooth separation and induction whether patients are coming to the OR from the ED or ICU. Midazolam (0.5–1.0 mg/kg) may be given orally or intravenously with adequate nurse supervision and in the absence of respiratory symptoms. Heavy premedication may be warranted to avoid agitation in patients with Moyamoya Syndrome or an intracranial aneurysm/arteriovenous malformation that has recently hemorrhaged. Opioids may be withheld preoperatively, since they may cause nausea or respiratory depression, especially in patients with increased ICP. Any administration of sedatives or analgesics that depress mental status merits close clinical observation and pulse oximetry in the child who will undergo neurosurgery.

General Principles of Intraoperative Management

General anesthesia is typically described to have three phases: induction, maintenance, and emergence. Typically, the patient's preoperative status will dictate the appropriate technique and medication choices for all phases of general anesthesia.

Induction Phase of Anesthesia

In the presence of intracranial hypertension, the primary goal during induction is to minimize severe increases in ICP. In general, most intravenous drugs decrease CBF and metabolism and ICP. Thiopental (4–8 mg/kg) or propofol (2–5 mg/kg) have similar effects on cerebral hemodynamics and maintain tight coupling of CBF and CMR. Patients at risk for aspiration pneumonitis (including certain patients with high ICP) should have a rapid-sequence induction of anesthesia using cricoid pressure. An intravenous hypnotic drug such as thiopental or propofol is given and then immediately followed by a rapid acting muscle relaxant. Rocuronium can be used when succinylcholine is contraindicated, such as for patients with spinal cord injuries or paretic extremities. In instances of pre-existing neurologic injury such as a patient with a history of a stroke resulting in a weak extremity, succinylcholine can result in sudden, catastrophic hyperkalemia. Etomidate and ketamine are frequently used to induce anesthesia in hemodynamically compromised patients, since these drugs are less likely to cause hypotension than thiopental or propofol. However, CNS excitation and increased ICP have been associated with these drugs respectively, and they may not be appropriate for many neurosurgical patients. Ketamine may be avoided because of its known ability to increase cerebral metabolism, CBF, and ICP in patients with increased ICP. Mask induction can be induced in certain situations when patients are neurologically stable. ICP can be lowered during induction with controlled hyperventilation and administration of an opioid and/or barbiturates before laryngoscopy and intubation. A non-depolarizing muscle relaxant may then be administered after intravenous (IV) access has been established to facilitate intubation of the trachea. As discussed above, succinylcholine should be avoided in patients with denervating processes such stroke, or spinal cord injury, since it can result in life-threatening hyperkalemia.

Airway Management

Developmental changes and the presence of genetic disorders/syndromes in airway anatomy have a significant impact on management of the pediatric airway. Nasotracheal tubes may be preferred for situations when there is no concern for basilar skull fractures and when the patient will be prone since orotracheal tubes can kink at the base of the tongue when the head is a flexed and result in airway obstruction. The timing of tracheal extubation may be challenging following neurosurgical procedures. Infants, particularly those with the Chiari malformation [158] or myelomeningocoele [159] or children after procedures in the posterior fossa [160] may exhibit intermittent apnea, vocal cord paralysis, or other irregularities before resuming a stable respiratory pattern. Significant airway edema and postoperative obstruction can complicate prone procedures or those involving significant blood losses and large volume replacement. Lingual or supraglottic swelling may require direct laryngoscopy to assess the airway. Head-up positioning and gentle forced diuresis usually improves airway edema within 24 h. The presence of airway edema post operatively may be impacted by intraoperative patient positioning (e.g., prone positioning for posterior fossa and spinal cord surgery). In addition to the physiological sequelae of the sitting position, a whole spectrum of neurovascular compression and stretch injuries can occur. . Postoperative visual loss has been linked to spine surgery. The etiology is unclear but, in adults, may be linked to prone positioning, surgical duration, surgical blood loss, anemia or hypotension. Challenges with intraoperative positioning include prevention of excessive neck rotation to prevent venous flow, and prevention of venous air emboli (VAE) [161, 162].

Vascular Access

The routine use of central venous catheters in pediatric neurosurgical patients is controversial. At a minimum, the anesthesiologist will use two large peripheral venous cannulae for most craniotomies. Should peripheral intravenous be difficult to secure, central venous access may be needed.

Since significant blood loss and hemodynamic instability can occur during craniotomies, an arterial catheter provides direct blood pressure monitoring and sampling for blood gas analysis.

Maintenance Phase of Anesthesia

Specific drugs utilized for the maintenance of anesthesia have not been shown to affect the outcome of neurosurgical procedures when properly administered [163]. The most frequently utilized technique during neurosurgery consists of an opioid (i.e., fentanyl, sufentanil or remifentanil) and low dose (0.2–0.5 %) isoflurane or sevofurane (<1 MAC). Administration of a preoperative benzodiazepine such as midazolam (0.5 mg/kg p.o., 0.1 mg/kg I.V.) in select patients should provide some degree of amnesia of perioperative events as well as minimize anxiety.

Chronic administration of anticonvulsant drugs, such as phenytoin and carbamazepine induces rapid metabolism and clearance of neuromuscular blockers and opioids, due to enhance activity of the hepatic P450 enzymes [122]. Patients receiving chronic anticonvulsant therapy will require larger doses of muscle relaxants and opioids because of induced enzymatic metabolism of these agents [164]. Muscle relaxants should be withheld or permitted to wear off when assessment of motor function during neurosurgery is planned, either intraoperatively or post operatively.

Monitoring

Intraoperatively, patients undergoing major craniotomies are at risk of sudden hemodynamic instability due to hemorrhage, venous air emboli (VAE), herniation syndromes, and/or manipulation of cranial nerves. Postoperative opening of central venous line ports may also place patients at risk for VAE. In addition to standard monitoring of electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring, the potential massive blood loss warrants placement of an arterial cannula for continuous invasive blood pressure monitoring as well as for sampling serial blood gases, electrolytes, glucose levels and hematocrit, in both the operating room and ICU. The utility of central venous catheterization remains controversial and there is no clear cut evidence suggesting the superiority of one location over the other. Concerns over the lack of adequate venous drainage with indwelling internal jugular lines sometimes leads clinicians to place lines in either the subclavian and or femoral vein, but these alternate sites are associated with complications such as pneumothorax and infection, respectively. Moreover, the diameter of the internal jugular vein is large enough to typically accommodate a central line and facilitate adequate venous drainage [165].

Advanced Neurophysiological Monitoring

Neurophysiological monitoring is commonly used in the intraoperative setting but is an emerging area of investigation in the ICU setting for diagnosis and prognostication. Recent advances in neurophysiological monitoring have enhanced the ability to safely perform neurosurgical procedures in functional areas of the brain and spinal cord. In general, electrocorticography (ECoG), electroencephalography (EEG), and somatosensory evoked potentials (SSEP) can be utilized with low levels of volatile anesthetics or ICU sedation. An anesthetic technique using high dose opioids and minimal inhaled agents (<1 MAC) is the most appropriate agent for this type of monitoring in the OR. Moreover, the use of sedatives should not be prohibitive to neuromonitoring in the ICU setting. Spinal cord and peripheral nerve surgery may require electromyography (EMG) and detection of muscle movement as an end-point, but muscle relaxation should be avoided or discontinued after tracheal intubation to facilitate monitoring. Motor evoked potentials (MEP) monitors the integrity of the motor tracts of the spinal cord by stimulating the motor cortex and detecting the action potentials in the corresponding muscle groups. Volatile anesthetic agents, including nitrous oxide, have a dose-dependent depressant effect on the MEPs, while intravenous anesthetic drugs (propofol, opioids, ketamine, and dexmedetomidine) typically preserve MEPs.

Somatosensory evoked potentials, electroencephalograms, and bispectral index are examples of neurophysiological monitors which have been used in the OR and ICU in critically ill children [166]. Of these, EEG is the most commonly used monitor for seizures and cerebral ischemia and has been intensively investigated. Electroencephalographic waveforms are the summation of excitatory and inhibitory postsynaptic potentials from the superficial layers of the cerebral cortex. Both regional and global ischemia results in profound depression of EEG activity, characterized by an attenuation of high-frequency activity and appearance of slow waves in the corresponding area. This feature makes EEG monitoring the most reliable intraoperative monitor for focal cerebral ischemia. Direct analysis of the raw EEG by an electrophysiologist remains the gold standard for monitoring cerebral ischemia. Conditions in which cerebral perfusion may be compromised can be monitored with scalp EEG electrodes or direct ECoG with subdural strip electrodes. Cerebrovascular disease is rare in infants and children, but two conditions in which EEG monitoring may be beneficial are temporary clipping of cerebral aneurysms and moyamoya disease. Cerebral aneurysm clipping can result in ischemia in the cerebral regions supplied by adjacent arteries. Direct electrocorticography in the region at risk can detect cerebral ischemic during test occlusion of the aneurysm and can serve as a guide for proper positioning of the aneurysm

clip and institution of pharmacological interventions of improved cerebral perfusion.

Cerebral Oxygenation Monitors

The primary cause of cerebral ischemia in infants and children is cerebral hypoperfusion secondary to systemic arterial hypotension or sustained intracranial hypertension. The major perioperative modalities for monitoring cerebral ischemia are: (1) jugular venous oximetry, (2) cerebral oximetry and, (3) brain tissue oxygenation.

Jugular Oximetry

Jugular bulb catheters may be inserted retrograde into the internal jugular using angiocaths for intermittent sampling or fiberoptic catheters for continuous readings and are a useful tool for determining cerebral oxygenation (jugular venous oxygen saturation, $SjvO_2$). Normal $SjVO_2$ ranges from 50–75 %; values at either extreme reflect global ischemia or hyperemia, respectively. $SjvO_2$ monitoring can provide early diagnosis of global ischemia and is useful to guide decisions for guiding and optimizing hyperventilation therapy, perfusion pressure, fluid management, and oxygenation in head injured patients [167, 168]. While $SjvO_2$ monitoring is not ubiquitous during craniotomies, it is routinely performed for most craniotomies at some institutions. Matta et al. [169] have demonstrated in adults that $SjvO_2$ monitoring detects critical intraoperative cerebral desaturation that would otherwise have been untreated, and Moss et al. [170] have used $SjvO_2$ monitoring to determine the minimum blood pressure that should be maintained to avoid hypoperfusion during aneurysm surgery [171].

Cerebral Oximetry

Near infrared spectroscopy (NIRS) provides a noninvasive assessment of cerebral intravascular oxyhemoglobin and deoxyhemoglobin (oxy-Hb and deoxy-Hb) and mitochondrial cytochrome oxygenation by measuring the abilities of these two chromophores to absorb near infrared light. Quantitative measurement of changes in cerebral chromophore oxygen concentration is related to the overall optical attenuation of NIR light, and has been used to assess oxygen delivery and extraction, cerebral blood volume, CBF (indicator dye technique), and the redox state of the brain. The NIRS correlated with mean arterial pressure and is effective in identifying premature infants with impaired cerebrovascular autoregulation [172]. The equipment used in these studies is primarily research prototype and is not commercially produced. Therefore, this technique has yet to find a niche in routine intraoperative monitoring. Regional cerebral oximetry (rSO~INVOS, Somanetics Corporation, Troy, MI) is a simpler NIRS modality that measures relative changes in oxygen extraction in the total blood volume of a small brain area. This technique uses two wavelengths to determine oxy-Hb and total cerebral hemoglobin concentration. Because approximately 75 % of the blood volume within the brain is venous, the cerebral oximeter measurement reflects venous oxy-Hb saturation and has been reported to correlate with jugular bulb saturation.

Brain Tissue Oxygenation (PbO_2)

Brain tissue oxygenation is best studied in children in the TBI population. Measuring oxygen tension in the brain, it provides a measure of brain ischemia. A PbO_2 <10 mmHg in severe pediatric TBI reflects cerebral ischemia and this technology has been used to guide blood transfusion and prognosticate outcome in pediatric TBI [173]. Increasing normobaric oxygenation increases PbO_2 values in children with severe TBI but the response is variable. Currently, PbO_2 monitoring is an emerging advanced neruomonitor.

Anatomic Imaging and Cerebral Perfusion

Computed tomography (CT) is the mainstay of imaging during the preoperative and immediate postoperative periods. Indications for CT scans include timely diagnosis of lesions that cause increased ICP, detection of blood and the need for neurosurgery. Postoperative head CT scans are typically performed to exclude new onset hemorrhage post procedure. Intraoperative CT scans are available in some centers which obviates the need for transporting neurosurgical patient during the immediate postoperative period. Neurosurgical patients may be exposed to a large number of head CT scans during the perioperative period, which causes unwanted exposure to radiation. Concerns over the lifetime attributable risk of cancer from medical imaging, especially in the developing brain, from head CT scans have been raised by individual investigators [174] as well as national organizations which have campaigned to reduce unnecessary radiation exposure to children [175]. Early MRI scanning has been suggested as an alternative to head CT scans, especially in cases of suspected inflicted injury [176]. Advanced CT based techniques to examine cerebral perfusion are available but at present are constrained by radiation dose concerns. Arterial spin labeling and advanced MRI techniques provide estimates of changes in CBF and CBV and bedside transcranial Doppler technology measures cerebral blood flow velocity and is an appealing modality of evaluating cerebrovascular hemodynamics at the patient's bedside and with no radiation risk.

Emergence Phase of Anesthesia

In critically ill children, when patients are taken from the operating room to the ICU with residual anesthesia or sedation and an indwelling tracheal tube, there is no emergence phase of anesthesia.

Special Considerations for Perioperative Management of Select Neurosurgical Diseases

Congenital Anomalies

Congenital anomalies of the central nervous system generally occur as midline defects. This dysraphism may occur anywhere along the neural axis, involving the head (encephalocele) or spine (meningomyelocele). The defect may be relatively minor and affect only superficial bony and membranous structures or may include a large segment of malformed neural tissue.

Encephalocele

Encephaloceles are neural tube defects that present as protrusions of brain and CSF arising from the occiput to the frontal area. They can even appear as nasal "polyps" if they protrude through the cribriform plate. Large defects may present challenges to tracheal intubation. Significant blood loss can develop during surgical excision of these anomalies, especially if venous sinuses are entered. Adequate intravenous access should be ensured and blood products should be available.

Myelodysplasia and Spinal Cord Defects

Defects in the spine are known as spina bifida. If a bulge containing CSF without spinal tissue exists, it is called a meningocele. When neural tissue is also present within the lesion, the defect is called a meningomyelocele. Open neural tissue is known as rachischisis. Hydrocephalus is usually present when paralysis occurs below the lesion and is usually associated with an Arnold-Chiari malformation. Airway management, mask fit, and intubation may be difficult in infants with massive hydrocephalus or very large defects. Blood loss may be considerable during repair of a meningomyelocele when large amounts of skin are to be undermined to cover the defect. Patients with myelodysplasia are at high risk of developing allergic reactions to latex [157]. Postoperatively, respiratory status should be carefully assessed. Pulse oximetry is valuable during recovery from anesthesia because of difficulty with breathing after a tight closure, and because ventilatory responses to hypoxia are often diminished or absent in these patients when a Chiari malformation co-exists [177].

Spinal dysraphism is the primary indication for laminectomies in pediatric patients. Patients with myelomeningocele suffer from multisystem diseases that result from a severe injury to the developing CNS early in gestation. The systems involved may include the musculoskeletal system, genitourinary system and immune system in addition to the central nervous system. As mentioned above, these patients are at high risk of latex allergy. Insertion of an epidural catheter by the surgeon under direct vision can provide a conduit for the administration of local anesthetics and opioids for the management of postoperative pain. Other spinal anomalies (lipomeningoceles, lipomyelomeningoceles, diastematomyelias, and dermoid tracts) may manifest themselves as tethered cords. Children who have had a meningomyelocele repaired after birth may also develop an ascending neurologic deficit from a tethered spinal cord as growth occurs. EMG monitoring can be helpful for identifying functional nerve roots as described above.

Cerebral Palsy results in spasticity and severe spasticity can be surgically alleviated by a selective dorsal rhizotomy (SDR). SDR reduces spasticity by surgically dividing dorsal rootlets to diminish the afferent input to motor neurons in the spinal cord, thus decreasing the hyperactive active reflexes associated with spastic diplegia. Pathologic rootlets are identified by direct stimulation and noting the corresponding muscle action potential with EMG. Exaggerated action potentials can be elicited in innervated as well as other distal muscle groups. These abnormal rootlets are partially sectioned in order to decrease afferent nerve conduction. However, these rootlets can potentially contain sensory and proprioceptive fibers. Spinal cord reflexes can be quantified by measuring the Hoffman reflex as noted above. The postoperative care of these patients is completed by severe somatic incisional pain, dysasthesia and hyperesthesia of the affected limb and muscle spasms. A variety of post operative pain management techniques have been advocated in these patients. These include intravenous morphine and midazolam/diazepam infusions and epidural opioids [178].

Chiari Malformations

Chiari malformations are generally defined as an anatomical abnormality of the posterior fossa leading to cephalad displacement of the cerebellar vermis through the foramen magnum. There are four types of Chiari malformations. Type I occur in healthy children without myelodysplasia. These patients generally have much milder symptoms, sometimes presenting only with headache or neck pain, usually during adolescence. The Arnold-Chiari malformation (type II) almost always co-exists in children with myelodysplasia. This defect consists of a bony abnormality in the posterior fossa and upper cervical spine with caudal displacement of the cerebellar vermis and lower brainstem below the plane of the foramen magnum. Medullary cervical cord compression can occur. Vocal cord paralysis with stridor and respiratory distress, apnea, abnormal swallowing and pulmonary aspiration, opisthotonos, and cranial nerve deficits may be associated with the Arnold-Chiari malformation and usually present during infancy. Patients of any age may have abnormal responses to hypoxia and hypercarbia because of cranial nerve and brainstem dysfunction [179]. Extreme head flexion may cause brainstem compression in otherwise

asymptomatic patients. Type III Chiari malformations are associated with encephaloceles and have the most severe symptoms and long term disability. Type IV Chiari malformations are associated with absent cerebellum, and large posterior fossa cerebrospinal fluid spaces.

Tumors

Since the majority of intracranial tumors in children occur in the posterior fossa, CSF flow is often obstructed and intracranial hypertension and hydrocephalus is often present. The intraoperative period includes elevation of the bone flap which can result in sinus tears, massive blood loss, and/or VAE. Surgical resection of tumors in the posterior fossa can also lead to brainstem and/or cranial nerve damage. Damage to the respiratory centers and cranial nerves can lead to apnea and airway obstruction after extubation of the patient's trachea.

Brain tumors are the most common solid tumors in children [180]. Supratentorial tumors account for about 25–40 % of brain tumors in children, and supratentorial resection usually requires invasive monitoring and techniques to control elevated ICP. The majority of brain tumors in children are infratentorial, and include medulloblastomas, cerebellar astrocytomas, brainstem gliomas, and ependymomas of the fourth ventricle. Because posterior fossa tumors usually obstruct CSF flow, increased ICP occurs early. Presenting signs and symptoms include early morning vomiting and irritability or lethargy. Cranial nerve palsies and ataxia are also common findings with respiratory and cardiac irregularities, usually occurring late. Sedation or general anesthesia may be required for radiologic evaluation or radiation therapy and surgical resection poses a number of anesthetic challenges including positioning, arrhythmias and acute blood pressure changes, depressed respiration, as well as VAE and increased ICP.

Tumors in the midbrain include craniopharyngiomas, optic gliomas, pituitary adenomas, and hypothalamic tumors and account for approximately 15 % of all intracranial tumors. Hypothalamic tumors (hamartomas, gliomas, and teratomas) frequently present with precocious puberty in children who are large for their chronological age. Craniopharyngiomas are the most common perisellar tumors in children and adolescents and may be associated with hypothalamic and pituitary dysfunction. Symptoms often include growth failure, visual impairment, and endocrine abnormalities. Signs and symptoms of hypothyroidism should be sought and thyroid function tests measured. Steroid replacement (dexamethasone or hydrocortisone) is generally administered since the integrity of the hypothalamic-pituitary-adrenal axis may be uncertain. In addition, diabetes insipidus occurs preoperatively in some patients and is a common postoperative problem. A careful history usually reveals this condition preoperatively, especially if attention is focused on nocturnal drinking and enuresis. Evaluation of serum electrolytes and osmolality, urine-specific gravity, and urine output is helpful since hypernatremia and hyperosmolality, along with dilute urine, are typical findings. If diabetes insipidus does not exist preoperatively, it usually does not develop until the postoperative period. This occurs due to the adequate reserve of antidiuretic hormone in the posterior pituitary gland capable of functioning for many hours even when the hypothalamic-pituitary stalk is damaged intraoperatively. Postoperative diabetes insipidus is marked by a sudden large increase in dilute urine output associated with a rising serum sodium concentration and osmolality. Treatment can initially be with dilute crystalloid solutions to replace the urine output with careful attention to electrolyte measurements. However, urine output is usually so prodigious (up to 1 L/h in an adult) that an infusion of aqueous vasopressin (1–10 mU/kg/h) is best utilized with fluid input then carefully restricted to match urine replacement and estimates of insensible losses. If diabetes insipidus persists, intranasal desmopressin can be used to replace intravenous pitressin, since desmopressin generally needs to be administered only twice daily. Return of antidiuretic hormone activity a few days postoperatively may cause a marked decrease in urinary output, water intoxication, seizures, and cerebral edema if desmopressin is not discontinued and fluid administration not adjusted appropriately. Transsphenoidal surgery is generally only performed in adolescents and older children with pituitary adenomas. Since nasal packs are inserted at the end of surgery, patients should be fully awake prior to tracheal extubation and transported to the recovery room.

Approximately 25 % of intracranial tumors in children involve the cerebral hemispheres. These are primarily astrocytomas, oligodendrogliomas, ependymomas, and glioblastomas. Neurologic symptoms are more likely to include a seizure disorder or focal deficits. Succinylcholine should be avoided if motor weakness is present since it can cause sudden massive hyperkalemia. Nondepolarizing muscle relaxants and narcotics may be metabolized more rapidly than usual in patients receiving chronic anticonvulsants. Choroid plexus papillomas are rare but occur most often in children younger than 3 years of age. They usually arise from the choroid plexus of the lateral ventricle and produce early hydrocephalus as a result of increased production of CSF and obstruction of CSF flow. Hydrocephalus usually resolves with surgical resection. When lesions lie near the motor or sensory strip, a special type of somatosensory evoked potential monitoring called "phase reversal" may also be used to delineate these locations [181]. If cortical stimulation is planned to help identify motor areas, muscle relaxants must be permitted to wear off. Nitrous oxide and narcotics are usually sufficient to prevent patient movement during these periods.

Hydrocephalus

Hydrocephalus is the most common pediatric neurosurgical condition. It is a condition involving a mismatch of CSF production and absorption leading to increased intracranial CSF volume. The majority of cases of hydrocephalus are due to obstruction of CSF flow or inability to absorb CSF appropriately. Hemorrhage (neonatal intraventricular or subarachnoid), congenital problems (aqueductal stenosis) trauma, infection, or tumors (especially in the posterior fossa) can cause hydrocephalus. Hydrocephalus is classified as nonobstructive/communicating or obstructive/noncommunicating based on the ability of CSF to flow around the spinal cord in its usual manner. Unless the etiology of the hydrocephalus can be definitively treated, treatment entails surgical placement of a ventricular drain or ventriculoperitoneal shunt.

Intracranial hypertension or a decrease in intracranial compliance almost always accompanies untreated hydrocephalus in children. How much intracranial compliance exists and how acutely hydrocephalus develops are both instrumental in how severe the signs and symptoms of hydrocephalus will be. In the young infant, if hydrocephalus develops slowly, the skull will insidiously expand and the cerebral vault will expand. However in older children the cranial bones are fused or the cranium cannot expand fast enough and signs of impending herniation rapidly become apparent. The patient may become progressively more lethargic and develop vomiting, cranial nerve dysfunction, bradycardia, and ultimately death.

The approach to patients with symptomatic hydrocephalus should be directed at controlling ICP and rapidly relieving the obstruction. These patients may be vomiting and at risk for pulmonary aspiration. A rapid sequence induction of anesthesia with thiopental or propofol followed by succinylcholine or rocuronium is indicated in these situations. Hyperventilation should be instituted as soon as the trachea is intubated. Unless the etiology of the hydrocephalus can be definitively treated, treatment entails surgical placement of a ventricular shunt. Most shunts transport CSF from the lateral ventricles to the peritoneal cavity (ventriculoperitoneal shunts). Occasionally the distal end of the shunt must be placed in the right atrium or pleural cavity, usually due to problems with the ability of the peritoneal cavity to absorb CSF as in peritonitis. VAE can occur during placement of the distal end of a ventriculoatrial shunt.

Endoscopic third ventriculoscopy by way of a percutaneous flexible neuroendoscope is an alternative to extracranial shunt placement [182]. During these procedures, a ventriculostomy may be made to bypass an obstruction (such as aqueductal stenosis) by forming a communicating hole from one area of CSF flow to another using a blunt probe inserted through the neuroendoscope. Common locations for a ventriculostomy are through the septum pellucidum (so the lateral ventricles can communicate) or through the floor of the third ventricle into the adjacent CSF cisterns. Complications such as damage to the basilar artery or its branches or neural injuries can be life threatening when they occur, and the anesthesiologist should be prepared for an emergency craniotomy during these procedures. Bradycardia and other arrhythmias have been also reported in conjunction with irrigation fluids and/or manipulation of the floor of the third ventricle [183].

There are a few special situations involving shunts that critical care physicians and anesthesiologists should be familiar with. Children who develop a shunt infection usually have their entire shunt system removed and external ventricular drainage established. They return to the operating room for placement of a new system several days later after their infection has been treated with antibiotics. While an external drain is in place, one must be careful not to dislodge the ventricular tubing. In addition, the height of the drainage bag should not be changed in relationship to the patient's head to avoid sudden changes in ICP. For example, suddenly lowering an open drainage bag can siphon CSF rapidly from the patient, resulting in collapse of the ventricles and rupture of cortical veins. When transporting patients with CSF drainage, it is best to temporarily close the ventriculostomy tubing during these brief periods.

Slit ventricle syndrome develops in approximately 5–10 % of patients with CSF shunts and is associated with overdrainage of CSF and small, "slit-like" lateral ventricular spaces. Patients with this condition do not have the usual amount of intracranial CSF to compensate for alterations in brain or intracranial blood volume. Administration of excess or hypotonic intravenous solutions should be avoided in order to minimize brain swelling, because postoperative cerebral herniation have been reported after uneventful surgical procedures in these children [184]. Postoperatively, the patient's mental status should be monitored because of the possibility of the reobstruction of the shunt leading to life threatening hydrocephalus.

Craniosynostosis

Craniosynostosis is a congenital anomaly in which one or more cranial sutures close prematurely. It occurs in approximately one of every 2,000 births, with males affected more frequently than females. The craniosynostosis can involve one suture, or it may be very complex and be associated with a variety of syndromes. If left uncorrected, the deformed cranium can result in increased ICP and compression of brain, with potential neurologic sequelae [185]. Surgical correction is usually performed within the first months of life to achieve the best cosmetic results. This is because brain growth is very rapid during infancy, "pushing" the skull into a normal shape. Repair of cranio-synostosis may involve removal of one small strip of bone from the skull, or it may entail a

complete reconstruction of the calvarium. Although these operations are extradural procedures, significant blood loss from the scalp and cranium make these challenging anesthetic procedures. It is essential that adequate venous access for rapid blood administration is secured, especially if multiple sutures are involved during surgery and postoperatively. Antifibrinolytic drugs (tranexemic acid) may have some utility in these procedures [186]. However, seizures have been reported after the use of high doses in cardiac surgery, which may be due to the intrinsic ability of TXA to inhibit glycine receptors [187]. The incidence of VAE is also significant during these procedures [188]. Endoscopic strip craniectomies are associated with decreased blood loss, decreased surgical time, and improved postoperative recovery time during endoscopic strip craniectomy in neonates and infants [189, 190]. Tobias and colleagues reported a significant decrease in the incidence of VAE during this procedure [191].

Epilepsy

Epilepsy remains one of the most common neurologic disorders in children. Although a number of new pharmacologic interventions have shown promise in the medical management of childhood epilepsy, a large number of children continue to have intractable seizures and resort to surgical interventions in such situations. Chronic administration of anticonvulsant drugs, such as phenytoin and carbamazepine induces rapid metabolism and clearance of neuromuscular blockers and opioids by upregulating hepatic P450 enzymes [122]. Intraoperative neurophysiologic monitors can be used to guide the actual resection of the epileptogenic focus and general anesthetics can compromise the sensitivity of these devices [192]. If cortical stimulation is utilized to mimic the seizure pattern or identify areas on the motor strip, neuromuscular blockade should be antagonized.

A variety of techniques are utilized during the entire perioperative period to aid in localization of seizure foci. A major part of preoperative planning should include a through discussion of the modality and type of neurophysiological monitoring to be used during the surgical procedure. In patients with generalized seizures, precise localization of the seizure focus is essential to minimize postoperative functional deficits. This involves serial craniotomies. The first is insertion of intracranial grid and strip electrodes. EEG grids and/or strips and placed on the exposed cortical surface in order to accurately create a map that will to localize the seizure focus. The patient is then observed in an electrophysiology unit in order to map the location of the seizure foci and provide a "road map" for the neurosurgeon for the resection. In some cases, the patient is monitored over several days. Once a seizure map is generated, the patient returns to the operating room for definitive resection. Depending on the location of seizure foci, age, and development of the patient, the resection is performed under general anesthesia or via an awake craniotomy technique. It is imperative that candidates for an awake craniotomy be mature and psychologically prepared to participate in this procedure. Therefore, patients who are developmentally delayed or have a history of severe anxiety or psychiatric disorders should not be considered appropriate for an awake craniotomy.

Intraoperative and postoperative seizures are an uncommon but devastating complication. Prophylaxis in the perioperative period and aggressive treatment of new convulsions are well-recognized mainstays of care. While phenytoin is the agent used most commonly for prophylaxis, maintaining therapeutic serum levels can be challenging [193]. Levetiracetam is becoming increasingly common and in many instances supplanting phenytoin as the choice for postoperative seizure prophylaxis. Both drugs can administered intravenously but unlike phenytoin, administration of levetiracetam does not require following serum drug levels to monitor for toxicity. Alternative agents frequently used in pediatrics include phenobarbital, carbamazepine, and valproic acid. Status epilepticus can be treated with, lorezepam 0.1 mg/kg IV push over 2 min or diazepam 0.5 mg/kg PR are effective agents. Lorezapam may be repeated after 10 min and accompanied by fosphenytoin 20 mg/kg IV or IM if initial doses are ineffective. Phenobarbital 20 mg/kg is also an effective first line antiepileptic drug.

Vascular Malformations

Vascular anomalies are rare in infants and children. Most of these conditions are congenital lesions that present early in life. Large arteriovenous malformations (AVM) in neonates may be associated with high output congestive heart failure and require vasoactive support. Initial treatment of large AVMs often consists of several treatments involving intravascular embolization in the interventional radiology suite [194]. Operative management is commonly associated with massive blood loss. Ligation of an AVM can lead to sudden hypertension with hyperemic cerebral edema [195] and should be treated with vasodilators such as labetalol or nitroprusside. Postoperative angiography may be indicated in order to rule out any residual AVMs or vascular leaks. Since re-hemorrhage or stroke can occur during the postoperative period, strict blood pressure parameters should be set to avoid hypo- and hypertension.

Moyamoya syndrome is a rare chronic vaso-occlusive disorder of the internal carotid arteries that presents as transient ischemic attacks and/or recurrent strokes in childhood. The etiology is unknown, but the syndrome can be associated with prior intracranial radiation, neurofibromatosis, Down's syndrome, and a variety of hematological disorders including sickle cell disease. Medical management consists of antiplatelet medications, e.g., aspirin or

calcium channel blockers. Surgical management is aimed at improving blood flow to the ischemic area. The operation involves suturing a scalp artery onto the pial surface of the brain (pial synangiosis). The anesthetic management of these patients is directed at optimizing cerebral perfusion [196]. This includes assuring generous preoperative hydration and maintaining the blood pressure within the patient's preoperative levels. Maintenance of normocapnia is essential as well because both hyper- and hypocapnia can lead to steal phenomenon from the ischemic region and further aggravate cerebral ischemia [197]. Once the patient emerges from anesthesia, the same maneuvers that optimize cerebral perfusion should be extended into the postoperative period. Postoperative agitiation and pain should be aggressively treated to minimize hyperventilation and increases in cerebral metabolic demand.

Neurotrauma

The fundamentals of pediatric neurotrauma, including TBI, spinal cord injury, multiple trauma and inflicted injury are discussed elsewhere in this textbook. In brief, the perioperative management of pediatric neurotrauma consists of adhereing to published national guidelines. For severe TBI, recommendations of care are well described in the recently published 2012 Guidelines for Acute Care Management of Infants and Children with Severe TBI [198]. Neurotrauma and prevention of secondary insults after neurotrauma remains the mainstay of anesthetic and intensive care medicine except for when surgical decompression is needed. There are documented changes in cerebral hemodynamics that occur after TBI where systemic hypotension, cerebral hypoperfusion, impaired cerebral autoregulation may ensue. These secondary insults may lead to cerebral ischemia, cerebral hyperemia and poor outcomes [7, 26, 123, 167, 199–210]. It is important to note that the Pediatric Guidelines for Severe TBI do not contain data from the intraoperative period and hence the specific hemodynamic thresholds for treatment may or may not apply. However, at present, given the paucity of data, a target cerebral perfusion pressure of at least 40 mmHg should be targeted [211–214]. The choice of vasopressors to increase blood pressure and CPP may vary. One single center study suggests that norepinephrine might lead to a higher increase in CPP than phenylephrine or dopamine in children with severe TBI [215]. The management of increased ICP, including hyperventilation for severe TBI in children is also described elsewhere in this text and in the Pediatric Guidelines [198, 211, 216, 217]. Patients who have refractory high ICP may undergo decompressive craniectomy and or receive hypothermia. It is important to note, however, that hypothermia is associated with increased mortality in these patients [218].

Additional Considerations

Neuroendoscopy

Technological advances in minimally invasive endoscopic surgery have entered the neurosurgical arena. Since neuroendoscopic techniques are designed to minimize surgical incision, dissection, and blood loss, less aggressive fluid replacement and invasive hemodynamic monitoring is becoming the norm. Endoscopic strip craniectomies are associated with decreased blood loss, decreased surgical time, and improved postoperative recovery time during endoscopic strip craniectomy in neonates and infants [189, 190, 219]. Tobias and colleagues reported a significant decrease in the incidence of VAE during this procedure [191]. Endoscopic third ventriculostomy is another approach for the treatment of obstructive hydrocephalus in infants and children [220]. A flexible fiberoptic scope is inserted through a trocar and provides a working channel that allows the neurosurgeon to insert a ventricular catheter or make frenestrations. Despite the relative safety of this procedure, bradycardia and other arrhythmias have been reported in conjunction with lack of egress of irrigation fluids and/or manipulation of the floor of the third ventricle [183, 221]. Neurogenic pulmonary edema due to acute intracranial hypertension has also been reported with this procedure [222].

Pain Management

Physicians are typically taught that the brain feels no pain and that this is due to the fact that only the dura has pain receptors. Traditionally, concerns over opioid related respiratory depression have resulted in conservative pain control strategies, such as avoiding opioids and or the use of suboccipital nerve blockers or as needed opioids. The use of sedation may also decrease the ability to assess and accurately record pain and patients with extracranial disease states or conditions might have pain from those conditions. Yet, pain after craniotomy may be more common that previously recognized. Optimal perioperative pain control in neurosurgical patients may aid with lowering ICP, assure a favorable neurovascular milieu, and facilitate timely diagnosis of the neurological problem. In one meta analysis of RCTs data from a total of 519 adults, who received four treatment strategies (scalp infiltration [five RCTs], nerve scalp block [two RCTs], parecoxib [one RCT] and patient-controlled analgesia with morphine [one RCT]), the authors reported that scalp infiltration with local anaesthetic may provide adequate analgesia in the first few postoperative hours, and nerve scalp block may provide longer lasting analgesia for 6 h. Morphine was found to reduce total analgesic rescue doses with no significant effect on nausea and no other side-effects and there was no significant evidence

was found to support the use of parecoxib in the treatment of postcraniotomy pain [223]. In the only pediatric study on postcraniotomy pain in children, Teo et al. reported that while most patients do not have pain during the first 72 h after surgery, many patients have at least one episode of a pain score ≥3 and predicted by duration of procedure. Perioperative pain regimens vary and include parenteral morphine, paracetamol, oxycodone, codeine, tramadol and ibuprofen [224]. No firm recommendations on analgesic therapy following craniotomy can be made because the number of well performed RCTs is limited and the study populations are very small. However, evidence on scalp infiltration suggests an analgesic effect in the first few postoperative hours.

OR to ICU Handoffs and ICU Handoffs to OR

Communication between the preoperative, intraoperative, and postoperative teams is essential for optimizing outcomes of pediatric neurosurgical patients. Creating specified checklists that facilitate transfer of critical and anticipatory events between members of the health care team including nurses and physicians is essential to preventing adverse events and to capturing near misses in these patients. One study by Brannen and colleagues showed that three-fourths of the handoffs had agreement about the severity of the patient's illness but that there was low agreement about the most severe problem and the total problem lists between residents involved in the handoff communication. Attending physicians were able to identify more patient problems [225].

Conclusion

The perioperative management of the neurosurgical patient is complex and challenging, requiring a solid understanding of the patient, preoperative conditions, surgical procedure, anesthetic events and potential postoperative complications. Developmental age and gender related differences between patients add to the complexity and may impact the course and outcome of neurosurgical patients. Finally, tremendous coordination between the clinical care teams is critical to preventing adverse events in this vulnerable patient population.

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Perioperative Care of the Urology Patient

11

Carley Riley and Shumyle Alam

Abstract

In this chapter, we present three topics related to the care of the urology patient. In the first section, we describe the postoperative care of the complex urology patient. We subsequently discuss the care of the patient with neurogenic bladder and then provide a review of catheter-associated urinary tract infections, an essential consideration in the care of any patient requiring urinary catheterization.

Keywords

Pediatric urology • Anorectal malformation • Genitourinary repair • Neurogenic bladder • Urinary catheterization • Catheter-associated urinary tract infection

Introduction

In the last three decades, the field of pediatric urology has made considerable progress in the surgical and medical management of patients born with complex urological abnormalities, including anorectal malformations, cloaca, cloacal exstrophy, Eagle-Barrett Syndrome, and posterior urethral valves. Urinary tract reconstruction involves the treatment of the neurogenic bladder and bowel. The procedures most often performed include a bladder neck procedure, a Mitrofanoff neourethra, a bladder augmentation, and a Malone antegrade continence enema. Very often these procedures are performed with a laparotomy, but a few centers are now attempting urinary tract reconstruction in a minimally invasive fashion. Often these patients have undergone prior transperitoneal surgery and have longer operative times than the less complicated myelomeningocele or exstrophy patients.

Following urinary tract reconstruction, patients require postoperative management in the Pediatric Intensive Care Unit (PICU) for a variety of reasons. Some of these patients also have chronic kidney disease, which may compound the complexity of their intraoperative and postoperative care. The age, pre-surgical state of health, and prior postoperative history of the patient along with the length, complexity, and invasiveness of the surgery are considerations that influence the decision to provide immediate postoperative monitoring and care in the PICU [1]. In most, but certainly not all cases, these patients require less than 24 h in the PICU and are usually discharged to home from a non-intensive care unit within 7–10 days after surgery [2]. However, as with other critically ill postoperative patients, primary concerns include cardiorespiratory monitoring, fluid and electrolyte management, pain management, and monitoring for surgical complications.

Some urology patients never require admission to the PICU. For example, the postoperative care of children with myelomeningocele is fairly straightforward. Moreover, renal injury in this patient population is now rarely seen since the initiation of aggressive management of the lower urinary tract after birth [3]. Bladder augmentation is also less frequent due to the judicious use of anticholinergics early in the

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neonatal period [4]. Patients that do not require bladder augmentation often do not require intensive care even in the immediate postoperative period. As a result, many of these patients are able to recover in a non-intensive care ward after surgery.

When a patient with a neurogenic bladder requires admission to the PICU for any other indication, the PICU team must understand the routine care and baseline needs that influence the plan of care. The goals of management for the child with neurogenic bladder involve maintaining a low-pressure bladder, minimizing risk of infection, and preserving the function of the upper urinary tract. Though clean intermittent catheterization has been recognized as the preferred method for routine urinary catheterization, indwelling catheterization is common in the PICU setting. Implications of both methods are discussed. Moreover, special consideration is necessary when managing suspected or confirmed infection in these patients.

Urinary catheterization, a necessary component of care for many patients both with and without neurogenic bladder, is associated with increased risk of urinary tract infection among other complications. Catheter-associated urinary tract infection, the most frequent healthcare-associated infection, may result in significant mortality, morbidity, and additional healthcare costs. Many infections can be prevented through systematic application of multiple different interventions. Strategies that target minimal use of indwelling urinary catheters and universal adherence to good infection control practices decrease the incidence of this healthcare-associated infection.

General Perioperative Considerations

Airway Management

After complex urologic surgery, some patients benefit from continued mechanical ventilation. Older patients may achieve adequate pain control without respiratory depression through the use of epidural anesthesia or patient-controlled analgesia, but younger patients often require 24–48 h of mechanical ventilation to allow for adequate analgesia and sedation in the immediate postoperative period. Especially in the case where osteotomies are performed for exstrophy closure. Patients may also require continued mechanical ventilation depending on their postoperative fluid status, their continued fluid management needs, and other pre-existing chronic conditions.

Some patients with anorectal malformations will have associated airway pathology and require a thoughtful plan of care established prior to surgery regarding airway management in the post-operative setting. The PICU physician must communicate with anesthesia and the prior airway surgeon regarding that plan. For select patients, pulmonary medicine specialists may be involved in this management.

Fluid and Electrolyte Management

Prior to complex urologic surgeries including bladder augmentation, patients are often admitted to undergo preoperative bowel preparation. These patients then experience prolonged operative times during which they experience substantial insensible fluid losses. As a result of the preoperative care and intraoperative experience, the perioperative fluid losses are generally high. It is imperative that the pediatric intensivist understands this issue in order to prevent dehydration in the postoperative period.

Attention to fluid management is crucial to the care of the reconstructed urologic patient not only because the risk of dehydration is high, but also because dehydration in the immediate postoperative period may have particularly disastrous consequences in this context. When bladder augmentation is necessary, the bowel segments used include ileum, colon, or stomach. The blood supply of the augment and Mitrofanoff is usually by a pedicle from the mesentery of the bowel. Venous stasis due to dehydration could result in thrombosis and loss of the segment.

Monitoring for electrolyte and acid-base imbalances is also important for the patient who has a segment of the gastrointestinal tract within the urinary tract, because the gastrointestinal mucosa may lead to particular disturbances after it is incorporated in the urinary tract. Ileal and colonic segments result typically in a hyperchloremic metabolic acidosis (Table 11.1). Renal injury may exacerbate this acidosis.

For ileal conduits that are urinary diversions, this acid-base disturbance is thought to result from the active exchange of ammonium chloride for carbonic acid by a cyclic AMP-dependent chloride pump. To address the acidosis, sodium bicarbonate is often trialed first, but medications that inhibit cyclic AMP, such as chlorpromazine or nicotinic acid, may be utilized. For bladder augmentation using ileal segments, this complication occurs in 15–20 % of patients, though not all patients require medication. With colonic segments, hypokalemia with total body potassium depletion may also occur, but the imbalances associated with colonic segments are typically mild. This of course may be worse in the setting of a previously known type IV renal tubular acidosis (RTA). Jejunal segments tend to lead to hyperkalemic, hyponatremic metabolic acidosis (Table 11.1). Because the jejunum has a very highly absorptive surface, use of jejunal segments in the urinary tract can cause severe metabolite shifts. As a result, jejunal segments are typically avoided. Gastric reservoirs typically result in hypochloremic metabolic alkalosis (Table 11.1) due to the ability of the gastric mucosa to acidify the urine and lead to a resultant net chloride ion excretion. For this reason, urologists may use gastric and bowel segments in combination in efforts to balance each type of segment's adverse effects. Because these different segments can lead to important electrolyte and acid-base imbalances,

Table 11.1 Metabolic disturbances associated with gastrointestinal segments in the urinary tract

Gastrointestinal segment	Associated metabolic disturbance
Stomach	Hypochloremic metabolic acidosis
Jejunum	Hyperkalemic, hyponatremic metabolic acidosis
Ileum	Hyperchloremic metabolic acidosis
Colon	Hyperchloremic, hypokalemic metabolic acidosis

the pediatric intensivist should be aware of the implications of the use of the gastrointestinal tract as a urinary conduit. In addition the use if proton pump inhibitors or H2 blockers is very important in the post-operative management of these patients.

Fluid and electrolyte management can be even more complicated because the complex urology patient that would need to recover in the PICU also often has some degree of CKD. In patients with a history of obstructive uropathy, fixed urine output as well as type IV RTA may occur. Fluid management for these patients therefore requires unique considerations, yet optimal fluid management for this population has not yet been described in the medical literature. The vast majority of these patients have intravenous fluid rates titrated to maintain a minimum of 1–2 mL/kg/h urine output. Importantly, the composition of this fluid remains simple for the first two postoperative days, so it may be manipulated easily in response to the patient's needs.

Because the child with neurogenic bladder and renal injury may have a fixed urine output and concentrating deficit, it is necessary for the pediatric intensivist to understand the baseline urine output of the child. In this circumstance, the baseline urine output in mL/kg/h should guide postoperative fluid management. This baseline urine output may be well above the estimates 1–2 ml/kg/hr. This is typically the case in the setting of the child with obstructive uropathy. Knowledge of the patient's baseline urine output is mandatory before attempting reconstruction for several reasons. This knowledge:

Allows for guidance regarding peri-operative fluid management,

Serves as a guideline for creating an appropriate size reservoir to allow for 4 h of urine storage, and

Is essential for the post-operative fluid management in the ICU, especially when the patient experiences post-operative fluid shifts.

Knowledge of baseline weight and use of daily weights during the postoperative period also helps guide fluid management. Ideally, this cumulative knowledge guides the surgeon and anesthesiologist prior to starting surgery. If not, the child can have profound fluid and base deficits when brought to the PICU for post-operative care. Per usual practice, however, the clinician may provide the patient additional fluids depending on the patient's vital signs, intake and output, and serial blood gas and electrolyte values. The patient may also receive fluids to replace surgical drain output, but in most cases replacing the nasogastric suction output is sufficient [1].

Nutrition

Total parenteral nutrition (TPN) after surgery remains a controversial topic. In general, if a decision to use TPN is made, it is not initiated until the second or third postoperative day. This delay is critical in the patient with CKD and possible type IV RTA because this patient's electrolytes may vary widely in the postoperative period depending on the complexity of the surgery. It is best to start TPN only after the patient's fluid and electrolyte status has stabilized.

Drain Management

Complex urology patients may have one or more drains to monitor in the postoperative period. Urethral catheters are common. Suprapubic catheterization is also common and involves insertion of a catheter through an incision in the abdominal wall and directly into the bladder [5]. A patient may also have a Mitrofanoff and/or Malone. It is essential that the pediatric intensivist understands these drains, their expected drainage, and their potential complications in the immediate postoperative period. Failure to understand the precise locations of the drains as well as expected urine volume can lead to disastrous complications including rupture of the bladder in the immediate post-operative period. Care must be taken to secure the catheters and tubing such that they cannot be accidently dislodged or obstructed. Stoma sites should be checked every shift and catheter securement verified with every nursing assessment. The tubes also drain differently depending on their position. Typically, the suprapubic catheter is the largest and often the most gravity dependent, so urine may flow preferentially from this tube.

In 1980, Paul Mitrofanoff described the "trans-appendicular continent cystotomy" for use as an alternative conduit for bladder catheterization when the urethra was not available [6]. The appendix remains the preferred conduit, but if it is unavailable, alternative conduits may be used. The most commonly utilized alternative is a segment of ileum that has been opened and then closed transversely [1, 6]. These conduits provide a continent channel for clean intermittent catheterization through an easily acceptable stoma into a bladder or other good capacity, low pressure reservoir. The stoma for this conduit is most commonly placed in a cosmetically acceptable location with easy access by the patient's dominant hand, typically either in the umbilicus or in the right or left lower quadrant of the abdomen [6]. The indwelling catheter must be well secured and free from

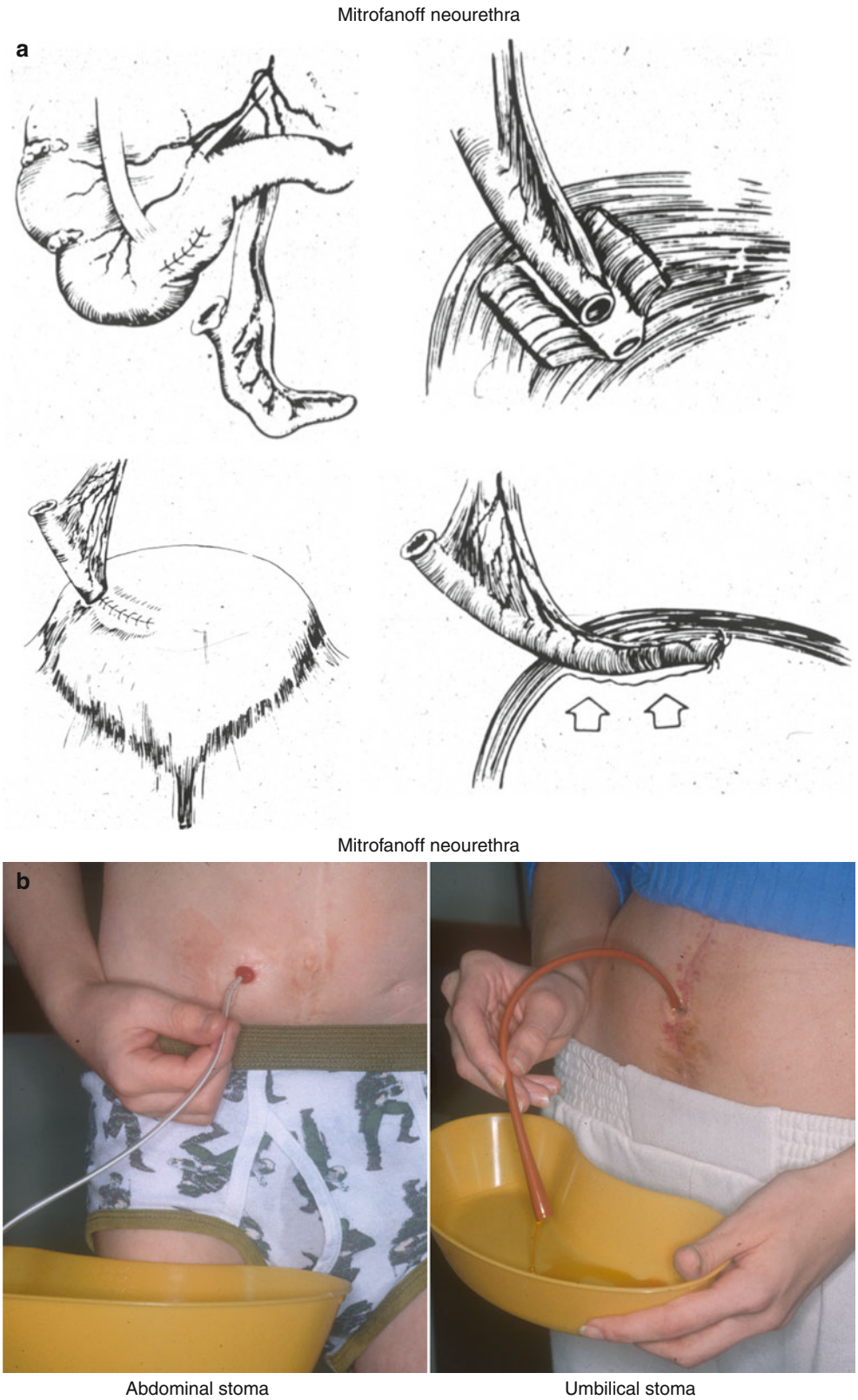

Fig. 11.1 (**a**) Illustration of steps involved in creating a Mitrofanoff neourethra, a conduit for catheterizing the bladder without passing a catheter through the urethra. (**b**) Two examples of Mitrofanoff stomas through which the boys are emptying their bladders through a stoma in their bellies

tension especially at the level of the skin because pressure at the stoma may increase the risk of stomal stenosis after surgery (Fig. 11.1a, b).

The Malone, or Malone Antegrade Continence Enema (MACE), is used to manage fecal soiling and intractable constipation, typically in patients with myelomeningocele or

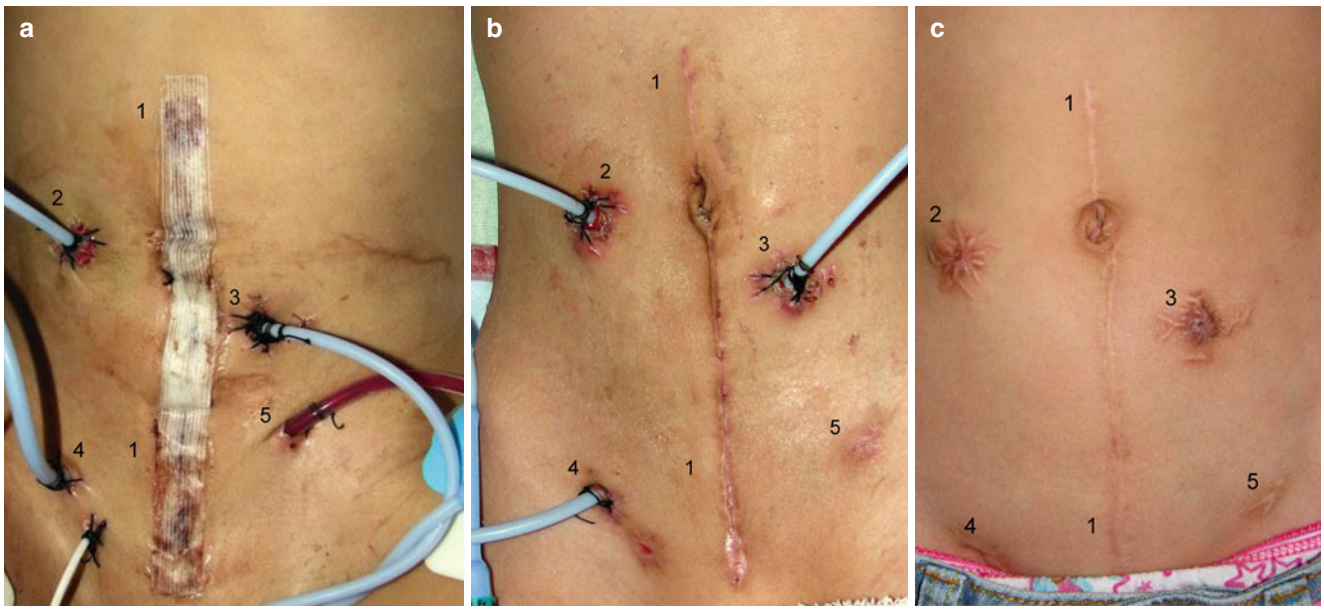

Fig. 11.2 (**a**) Immediately after bladder neck reconstruction, Malone, and Mitrofanoff. Sites of the: (*1*) abdominal incision, (*2*) Malone, (*3*) Mitrofanoff, (*4*) suprapubic catheter, and (*5*) Jackson-Pratt drain. (**b**) Days after bladder neck reconstruction, Malone, and Mitrofanoff. Sites of the: (*1*) abdominal incision, (*2*) Malone, (*3*) Mitrofanoff, (*4*) suprapubic catheter, and (*5*) Jackson-Pratt drain. (**c**) One and a half years after bladder neck reconstruction, Malone, and Mitrofanoff. Healed sites of the: (*1*) abdominal incision, (*2*) Malone, (*3*) Mitrofanoff, (*4*) suprapubic catheter, and (*5*) Jackson-Pratt drain

anorectal anomalies. The surgical technique for creation of the Malone is an adaptation of the Mitrofanoff technique. Either the appendix, transverse ileal segment, or a flap of colon is implanted to allow for regular colonic washouts. In the postoperative period, this conduit remains catheterized to allow for optimal healing, and enemas are initiated after return of bowel function [1]. In general, flushes are not started in the immediate post-operative period especially if there is a bowel anastomosis.

The urinary catheters, including Foley, suprapubic, and Mitrofanoff, are placed to gravity drainage and monitored closely for urine output [6]. After implantation of the appendix for either Mitrofanoff or Malone conduits, mucus produced by the appendical lining falls into the bladder where it may lead to obstruction [1]. Therefore, during the postoperative course, decreased or absent urine output from one or more of the urinary catheters most likely represents mechanical obstruction of the outflow tract. Aggressive monitoring of urine output is necessary during this period. If urine output drops, it is often necessary to irrigate the catheters gently with a low volume of sterile saline. Failure to recognize an occluded catheter can result in perforation and the need for reoperation. While either mucus or blood can occlude the catheters in the immediate post-operative period, stone formation is generally a consequence of stasis and infection and is not seen in the immediate postoperative period (Fig. 11.2a, b).

After bladder neck reconstruction, a catheter is generally left in the urethra. Here at Cincinnati Children's Hospital Medical Center (CCHMC), urologists utilize a circle stent. The stent is a small, usually 8 French silastic catheter that traverses the bladder neck through the bladder and urethra. One end is brought out through the abdomen and the other through the urethra. The ends are secured to themselves, hence the moniker "circle stent". The care of this catheter is routine. Since it does not drain urine, it is generally covered with a clear dressing.

The use of nasogastric tubes is controversial after bowel surgery. The tube has a slightly different role in the urologic patient. In the setting of a gastric segment for either augmentation or a neobladder, there will be an almost circumferential suture line on the stomach. In fact only the lesser curvature is spared in this procedure. The nasogastric tube is placed surgically and the tip oriented distally to the suture line. At CCHMC, the practice is to secure these tubes utilizing a modification of a bridle. These tubes should not be manipulated and if dislodged may require fluoroscopic guidance for replacement.

A nasogastric tube also provides decompression, so the bowels do not fill with air after surgery. If gaseous distension is allowed, though it will not harm the anastomosis, it can have an effect on the pedicles to the grafts. The tubes are set to low intermittent suction as copious bilious output is not anticipated in this setting.

Pain and Sedation Management

Management of pain and sedation is a primary concern. As discussed earlier, patients may require continued mechanical ventilator support to allow for adequate pain control in the immediate postoperative period. In these cases, pain and sedation management may include parenteral infusions of an opioid and a benzodiazepine. In patients greater than 1 year of age, epidural catheters may provide intraoperative and postoperative analgesia [1]. In the extubated patient, epidural medication may provide adequate analgesia. Oftentimes, however, epidural analgesia may not be utilized in the urologic patient due to the patient's associated spinal malformations such as tethered cord. If epidural analgesia is not used or remains inadequate, pain relief may be provided with parenteral narcotics, either nurse delivered or patient controlled.

For the complex urology patient, medications to relieve bladder spasm, such as diazepam and oxybutynin, are vital for optimal pain management. Medications to relieve muscle spasm, anxiety, and nausea are also important in the postoperative care of these patients. Since many of these patients, especially the gastric augment patients, can receive nothing enterally, diazepam is the drug of choice in the postoperative period. Caution should be utilized before delivering any pain or spasm medication per rectum. In the setting of a bladder neck reconstruction, urologists prefer avoiding any per rectum medication.

There is a unique group of patients who also require osteotomy at the time of urologic reconstruction. These patients include patients with cloacal exstrophy or bladder exstrophy whose closure was staged or delayed as well as patients with complex cloaca or urogenital sinus anomaly that has had the pubis divided in the midline to close the bladder neck. When possible, these patients benefit from epidural anesthesia. Otherwise, pain control must be carefully administered often with the help of an anesthesiologist. Over-sedation from aggressive pain management can have serious consequences.

Other Considerations

In the postoperative period, prophylactic antibiotics are chosen based on the surgery performed and the patient's antibiotic history. These antibiotics are initiated within 1–2 h of the surgical incision depending on the antibiotic used and are typically continued for several days, depending on the clinical course and the surgeon's preference [7]. Fever in the initial one to two postoperative days is often attributed to benign, noninfectious etiologies. Clinical assessment of the patient is essential, but cultures and broadened antibiotic coverage are often unnecessary. After the first 48–72 h, the occurrence of fever is more concerning for the presence of infection and therefore demands more thorough investigation and serious consideration of empiric broadening of antibiotic coverage [1].

The vast majority of these patients do not require transfusion of blood product in the postoperative period. The clinically stable patient may tolerate hemoglobin values as low as 7 g per deciliter [8]. The clinical course of the patient, however, influences the decision to transfuse [1]. This is especially true in the case of the child with CKD who may eventually require renal transplantation.

Many of these patients undergoing complex urinary tract reconstruction will require central vascular access. Many institutions favor peripherally inserted central catheters (PICC) line placement. If other central venous access is needed, the surgical team should be included in the decision-making process. Care must be taken regarding choice of access in the setting of a patient that will eventually require a kidney transplant. Moreover, some patients with cloacal and urogenital sinus malformations have aberrant iliac anatomy, so femoral lines may be contraindicated [9].

Most postoperative complications are anticipated based on the intraoperative course [1]. The pediatric intensivist therefore should seek anticipatory guidance regarding potential complications from the surgical team. A safe transition or hand-off of care from the (OR) to the PICU should involve all members of both the OR (including both the urologist and the anesthesiologist, as well as the OR nurse) and PICU teams. A formalized, comprehensive, face-to-face hand-off is most effective. During this safe handoff, the accepting ICU team learns of the patient's unique needs, including but certainly not limited to any concerns regarding fluid status, baseline urine output and anticipated urine output goals, and possible surgical complications that may become evident in the postoperative period. Through this dialogue, the surgical team and the PICU team may begin their partnership to provide optimal care to the complex urology patient.

Care of Patients with Neurogenic Bladder

The pediatric intensivist cares for children with neurogenic bladder during the postoperative period as described above as well as during hospitalizations for other medical and surgical reasons. When a patient with neurogenic bladder requires admission to the PICU, it is important that the PICU team understand the patient's routine care and baseline needs that influence the plan of care. Neurogenic bladder refers to the inability to store or empty urine [10]. Many congenital diseases are associated with the development of neurogenic bladder in the pediatric population, with myelomeningocele being one of the most common [10]. If the bladder is unable to empty normally, the post-void residual is increased which can contribute to urinary tract infection, urinary calculi from stasis, and overflow incontinence. Over the long term, vesicoureteral reflux and hydronephrosis may develop leading to further damage to the bladder and the upper urinary tracts [10, 11]. The goals of management for the child with

neurogenic bladder involve maintaining a low-pressure bladder, minimizing risk of infection, and preserving the function of the upper urinary tract [11]. These goals are achieved through implementation of a bladder management program including clean intermittent catheterization and anticholinergic therapy.

Intermittent Versus Indwelling Catheterization

For patients with neurogenic bladder, a bladder management program is a necessary component of their routine care. Intermittent catheterization is the mainstay of therapy for patients with neurogenic bladder. When the bladder is emptied through intermittent catheterization on a regular basis, over-distention of the bladder, residual urine, and increased intravesical pressures are avoided [10]. Though indwelling catheterization would also reduce distention and intravesical pressure, intermittent catheterization has become the preferred method of catheterization in patients with neurogenic bladder [10]. When studied in patients with neurogenic bladder secondary to spinal cord injury, intermittent catheterization improved bladder emptying, reduced the incidence of both urinary tract infection and urinary incontinence, and preserved renal function, cumulatively resulting in better outcomes [10]. As a result, recent guidelines from the Centers for Disease Control and Prevention encourage the use of intermittent catheterization in children with myelomeningocele and neurogenic bladder in order to decrease the risk of urinary tract deterioration [10].

Intermittent catheterization has a lower risk of infection when compared with indwelling catheterization, but the risk is not completely eliminated. Different methods for intermittent catheterization have been studied, including sterile and clean techniques as well as the use of single-use and multiple-use catheters, and no method has proven superior with regards to infection risk [11]. In the pediatric population, catheterization by a parent or other caregiver is common though children as young as 5 or 6 years of age have been taught to perform self-catheterization [5].

It is very important to note that the risk of having a positive urine culture while on intermittent catheterization approaches 70 % [12]. This does not mean, however, that all positive cultures represent infection. The tendency to obtain routine urinalysis and urine culture for patients on a catheterization program should be avoided since there will be a tendency to over-treat. Instead specific symptoms should warrant evaluation and treatment; these symptoms include pain with catheterization, blood in the urine, new-onset incontinence between catheterizations, or unexplained high fevers.

The most frequent complication of clean intermittent catheterization is infection, but other complications include urethral bleeding, urethral injury, inflammation, epididymal orchitis, stricture, diverticuli, and fistula formation [10, 11]. Research has demonstrated, however, that patients with a strong understanding of intermittent catheterization technique who adhere to a rigorous catheterization schedule have fewer urinary tract infections [10].

In the intensive care setting, however, indwelling catheter use is common. There are multiple indications for use of indwelling catheterization such as close monitoring of urine output and ensuring continual bladder decompression. There are also surgical indications for indwelling catheterization such as maintaining newly created urinary conduits in the postoperative period. As soon as medically and surgically appropriate, however, patients with neurogenic bladder should be transitioned to intermittent catheterization.

Antibiotic Use

The routine use of either prophylactic or treatment antibiotic for the patient admitted to the PICU with a history of intermittent catheterization is not recommended. The guidelines are straightforward in the perioperative setting but should not be applied to the routine use of antibiotics in this patient population. If a symptomatic UTI is suspected, culture specific antibiotics should be utilized. If pyelonephritis is suspected, broad-spectrum antibiotics are suggested in this patient population. Broad-spectrum antibiotics should be chosen based on an individual hospital's antibiogram.

Regardless of the indication for antibiotic use, consideration must be given to the antibiotic choice and dosing regimen in this patient population. For example, caution is suggested when treating the patient with a history of neurogenic bladder when admitted to the PICU with pneumonia. Some antibiotics commonly used for the treatment of community-acquired pneumonia will not be excreted by the kidneys and will not adequately treat an associated UTI.

The Augmented or Neo-Bladder

A prior history of augmentation or neobladder must be known. The metabolic disturbances seen with the use of intestinal segments are more likely to been seen well after the post-operative period as the urine is in contact with the segment of bowel for a longer period of time. Also, if a patient has had an augmentation and is dependent on catheterization as most are, care must be taken when rapidly hydrating the patient without a catheter. A bladder perforation can be a life-threatening event. The pediatric intensivist must know precisely the size and type of catheter used, especially in the setting of a Mitrofanoff, for the patient may be injured if a catheter is placed incorrectly or a balloon inflated in the incorrect position. This can, in some cases, destroy the operation. In these cases, a non-balloon catheter should be taped in position to drainage. In the setting where there is a concern or information lacking, urologic consultation is mandated.

Catheter-Associated Urinary Tract Infection

Though urinary catheterization is a necessary component of care for many patients both with and without neurogenic bladder, catheterization is associated with increased risk of urinary tract infection among other complications. Catheter-associated urinary tract infection is the most frequent healthcare-associated infection [13, 14] and causes preventable mortality and morbidity. It is also associated with considerable healthcare costs. Catheter-associated urinary tract infection comprises 35–40 % of all healthcare-associated infections [13, 14]. Though it is the most frequent healthcare-associated infection, catheter-associated urinary tract infection carries the lowest mortality and lowest cost burden [13]. Though urinary tract infection remains the most substantial adverse outcome of urinary catheter use, bacteremia and sepsis occur in a fraction of patients with catheter-associated bacteruria [15]. Other more minor adverse effects occur as well, including nonbacterial inflammation, urethral stricture, and mechanical trauma [15].

Most urinary tract infections that occur in the healthcare environment are associated with the use of an indwelling urinary catheter [15, 16]. Catheter-associated urinary tract infection is therefore common in part because the use of urinary catheters is common with 15–25 % of all short-term care patients using a urinary catheter during their hospital course [14, 17]. Some research estimates a 5 % increase in risk of bacteruria for every day of urinary catheter use [15, 17]. Other research finds that approximately one in four patients with an indwelling catheter will develop bacteruria within 2–10 days, and one in four of these patients will subsequently develop a urinary tract infection [16].

Two primary mechanisms of catheter-associated urinary tract infection have been described: (1) external ascent of bacteria that have colonized the external catheter surface such as could happen during insertion without aseptic technique and (2) internal ascent of bacteria through the catheter from bacteria contaminating the drainage system which could be introduced from improper handling of the system [17]. Common pathogens include *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Enterococcus*, *Proteus*, *Pseudomonas*, *Serratia*, coagulase-negative *Staphylococcus*, *Candida*, and *Acinetobacter* with *E. coli* as the most common in hospital-wide infections and *Candida* the most common in the PICU [16].

Among patients with urinary catheters, clinical manifestations of urinary tract infection are uncommon even with bacteruria [14]. These episodes are often treated with antibiotics independent of a patient's clinical status. However, bacteremia and sepsis can occur secondary to catheter-associated bacteruria. Historically, it has been estimated that 1–5 % of catheter-associated bacteruria episodes lead to secondary bacteremia, but it now appears that secondary bacteremia occurs less frequently than has been traditionally estimated. Even so, this mechanism nearly always involves gram-negative bacilli, making catheter-associated bacteruria the leading cause of hospital-acquired gram-negative bacteremia [14]. The mortality rate of patients with secondary bacteremia is approximated at 10 % [16]. Overall, however, the effect of catheter-associated bacteruria and urinary tract infection on mortality remains unclear with recent studies unable to demonstrate any increased risk of mortality [14, 18].

The healthcare costs associated with catheter-associated urinary tract infections are also uncertain. Estimated lengths of stay and healthcare costs attributable to catheter-associated bacteruria are highly variable [14]. Recent data suggest that treated episodes of catheter-associated bacteruria cost on average around $600 each and may not extend hospital stays by any appreciable amount of time [14, 17]. One source reports, however, that each episode of bacteremia secondary to urinary tract infection costs a minimum of $2,800 [17].

Though catheter-associated urinary tract infection has a low risk of mortality, appears to cause limited morbidity, and may result in minimal additional costs, the large aggregate numbers of episodes make catheter-associated urinary tract infection a clinically significant problem [15, 16]. Recognition of the importance of this infection has led to research and policy change to promote prevention of catheter-associated urinary tract infection. As of October 2008, the Centers for Medicare & Medicaid Services (CMS) designated catheter-associated urinary tract infection as one of the complications for which hospitals no longer receive reimbursement [17].

Prevention of CA-UTI

Many catheter-associated urinary tract infections are preventable. It may be that nearly 400,000 catheter-associated urinary tract infections and perhaps as many as 9,000 associated deaths may be preventable every year in the United States [16]. Recent research has therefore explored the best strategies for preventing this infection.

Because duration of urinary catheter use is the strongest predictor for the development of catheter-associated urinary tract infection, most prevention efforts focus first on limiting the use of indwelling urinary catheters [16]. The Association for Professionals in Infection Control and Epidemiology (APIC) published an Elimination Guide for Catheter-Associated Urinary Tract Infection that outlines interventions for circumventing or minimizing the duration of indwelling catheter use. Some of these interventions are:

- Using indwelling urinary catheters only when medically necessary,
- Assessing and documenting daily the need for catheterization,
- Utilizing reminder systems targeted at removing catheters,

- Considering intermittent catheterization instead of indwelling catheter insertion, and
- Removing promptly urinary catheters that are medically unnecessary [16].

Approximately one out of every four urinary catheters is unnecessary [19–22]. Research shows that initiatives to decrease unnecessary catheter use are effective and lead to lower rates of catheter-associated urinary tract infection [19–22]. As a result, many guidelines propose avoiding catheter use altogether and minimizing the duration of catheterization when indwelling catheter use is unavoidable [13].

Other measures to prevent catheter-associated urinary tract infection involve good infection control practices such as maintaining hand hygiene [13, 17], using aseptic technique for insertion of urinary catheters by trained healthcare providers [16, 17], and maintaining the drainage system appropriately [16]. Research also finds that measures to encourage removal of urinary catheters through procedure-specific guidelines for postoperative catheter removal, automatic stop orders for indwelling catheters, and/or daily reminder systems for review of catheter need also reduce rates of catheter-associated urinary tract infection effectively [15, 17, 23].

Creating and maintaining an appropriate infrastructure for surveillance, education, and training is vital to preventing catheter-associated urinary tract infection on an ongoing basis [17]. Implementing multimodal interventions by bundling practices together has shown to prevent catheter-associated urinary tract infection [17]. One strategy that has been studied but not shown to affect catheter-associated urinary tract infections rates significantly is the use of silver- or antimicrobial-coated urinary catheters. Reviews and meta-analyses have not yet produced evidence to support the routine use of these catheters. Recommendations therefore either do not include the use of these specially treated catheters or discourage uniform adoption of these catheters [14, 15, 24].

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Perioperative Care of the Orthopaedic Surgery Patient

12

Seirhei Slinko

Abstract

Children with orthopaedic problems frequently require post-operative care in the Pediatric Intensive Care Unit (PICU). Many of these children have complex medical conditions that necessitate care in the PICU. In other cases, the extent of surgery and/or intra-operative complications may dictate the level of monitoring and care required in the post-operative period. Major issues of concern to the pediatric critical care physician specifically include issues related to fluid and electrolyte management, post-operative respiratory insufficiency, and pain management. Effective recognition and appropriate management of all the aforementioned problems will improve outcomes and reduce the length of stay (LOS) in the hospital.

Keywords

Spinal fusion • Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) • Orthopaedics • Post-operative complications

Introduction

The practice of pediatric orthopaedic surgery has changed dramatically in the last decade. Ironically, progress in orthopaedic surgery, as well as in the other surgical subspecialties (e.g., cardiothoracic surgery) has been closely paralleled by advances in peri-operative care. As result, some orthopaedic interventions are performed on an ambulatory basis, using noninvasive general anesthesia with modern anesthetics and analgesics in combination with regional anesthesia techniques [1, 2]. However, as these advances have allowed more complex surgical procedures to be performed on patients with complex medical conditions, more children are requiring admission to the Pediatric Intensive Care Unit (PICU) following orthopaedic surgery. Importantly, the pre-, intra- and early post-operative periods should be considered as a continuum of care. The pediatric critical care physician is frequently involved in all phases along this continuum. Specific areas that are relevant to the PICU include issues related to fluid and electrolyte management, respiratory support, prevention of blood loss, and pain management.

Pre-operative Management

Pre-operative Evaluation

The extent of pre-operative evaluation of patients before orthopaedic surgery depends mostly on whether the child is previously healthy with relatively "simple" skeletal problems (e.g. fracture) or if the child has compromised function of one or more organ system(s) and more complex skeletal problems, such as neuromuscular scoliosis, that require long, technically challenging, and very invasive interventions in the operating room theater. The two extremes frequently, but not always, co-exist. For example, otherwise healthy adolescents with idiopathic scoliosis may require lengthy and invasive surgery. However, many of these same patients may not

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require post-operative care in the PICU. Conversely, a child with multiple medical problems and a seemingly simple surgical procedure may require care in the PICU.

There are four major factors that dictate both the method of anesthesia and the intensity of peri- and post-operative care and monitoring. The first factor is the presence vs. absence of congenital malformations, syndromes, and inherited conditions that commonly co-exist with orthopaedic disorders. For example, Klippel-Feil syndrome, achondroplasia, and arthrogryposis are characterized by limited cervical spine mobility and in each of these cases fiberoptic-assisted tracheal intubation should be considered. Second, many of these patients requiring orthopaedic surgery will have concomitant conditions affecting other organ systems, including hydrocephalus, cerebral palsy (CP), seizures, restrictive lung disease, mitral regurgitation, cardiac conduction system dysfunction, adrenal insufficiency, renal insufficiency, and obesity. In the case of CP with mental retardation, separation from the parents during the pre-operative evaluation may pose significant challenges. For children with seizure disorder, certain anesthetics, such as enflurane, etomidate, and ketamine should be avoided because they decrease the seizures threshold in these patients. In addition, careful consideration of when to stop taking seizure medications (for npo status) may require communication with the patient's neurologist. The third consideration (and a very important one) is whether the patient has a muscular dystrophy or congenital myopathy, for which depolarizing neuromuscular blockers should be avoided. The fourth and final consideration is the extent and length of the planned surgical intervention and estimated blood loss. Careful planning before the procedure will help to minimize blood loss and decrease transfusion requirements (see accompanying chapter on blood conservation).

In addition to a detailed review of past and current medical history, medications, and drug allergies, physical examination of all organ systems is strongly recommended. A thorough physical examination is especially important for most complicated skeletal deformities of the thoraco-lumbar spine, such as scoliosis. Progression of curvature and vertebral rotation leads to the development of a restricted thoracic cage with progressively worsening lung function, which may not resolve even after early corrective surgery [3]. Thoracic insufficiency syndrome is characterized by decreased vital capacity and generalized alveolar hypoventilation, decreased functional residual capacity, and hypoxemia. Progressive respiratory insufficiency in patients with scoliosis often required noninvasive ventilation support even before surgery [3, 4].

A thoracic insufficiency syndrome inevitably leads to severe dysfunction of the cardiovascular system. For example, hypoxemia, hypercapnia, and pulmonary vasculature remodeling cause pulmonary hypertension and cor-pulmonale. For these reasons, the complexity and severity of the anatomo-functional problems dictate special pre-operative tests before surgery, such as a chest radiograph, pulmonary function tests, arterial blood gas, spirometry and lung volumes, electrocardiogram (ECG), echocardiogram, coagulation studies, CBC, electrolyte panel, and liver function tests. The important point to emphasize is that a thorough evaluation and work-up before surgery will minimize the risk of complications during the intra-operative and post-operative period. Consultation with the child's medical specialists is particularly important. Finally, all of this information should be communicated to the pediatric critical care team.

Premedication

The major goal of premedication for children before any surgical intervention is the elimination of anxiety and fear. This is particularly relevant in children between the ages of 2–5 years, in whom the need for pharmacologic premedication is the highest. For children that undergo multiple, repetitive surgeries, such as often the case in patients with complicated muscular-skeletal pathology, previous experiences in the OR and hospital prior to the current procedure almost guarantee the necessity of an effective premedication that eliminates the aforementioned psychological reaction. The child's parents or guardians play an important role in this regard. Surprisingly, however, the presence of parents in the OR before the induction of anesthesia is of questionable benefit in studies performed to date. Not surprisingly, 80 % of parents whose children are undergoing surgery prefer to be present in the OR during the induction of anesthesia [5]. However, analysis of 14 studies (randomized controlled trials, prospective and retrospective comparative studies) showed that in most cases parental presence did not appear to alleviate either the parents' or child's anxiety [6, 7]. At the same time, this analysis showed that oral midazolam (dose 0.5 mg/kg administered 20–30 min preoperatively) is very effective in reducing both separation and induction anxiety in children [8]. Adding 3 mg/kg of oral ketamine to 0.5 mg/kg of midazolam resulted in early onset sedation, better anxiolysis, and early separation from a parent [9]. Multiple randomized controlled trials studies have found that midazolam is far superior to either a surgical preparation program or parental presence during induction of anesthesia in terms of perioperative anxiety and compliance during induction of anesthesia [10, 11]. Also, the use of clonidine in pediatric anesthesia appears to be a promising alternative to midazolam. For example, oral premedication with clonidine in doses 4–5 μg/kg in children provides an ideal level of sedation and anxiolysis, easy separation from parents, and a high acceptance rate of mask application. In addition, clonidine

reduces the incidence of post-operative vomiting and shivering, improves postoperative pain relief, and attenuates postoperative delirium [12]. Compared to benzodiazepines, clonidine does not causing anterograde and retrograde amnesia - instead it causes a state of sedation similar to normal tiredness-sleepiness [13].

Premedication for patients with poor cooperation that result from learning disability can be challenging, especially for children with co-existing CP or autism. The plan of premedication (medication choice and rout of administration) should be developed on the basis of information collected from the parents or caregivers who frequently may be more successful in delivering the premedication to the child than nursing staff. Specific information obtained in the preoperative evaluation, including the level of patient's cooperation, behavioral patterns, aggressiveness, and sources of anxiety, will help facilitate a safe and easy induction during the pre-operative period, as well as a smooth peri-operative period [14]. Common medications used in these patients include sedatives and anxiolytics (benzodiazepines) and neuroleptics (haloperidol) that may modify disruptive symptoms including hyperactivity and aggressiveness. Dosing studies for oral midazolam range from 0.25 to 1.0 mg/kg and demonstrated linear pharmacokinetic relationship up to maximum dose 20 mg [15] but this becomes nonlinear at higher dose. The higher doses provide faster onset of sedation and were not found to cause any adverse events [16]. In autistic children with behavioral disorders, compliance with induction was improved by adding ketamine compared with midazolam alone, without any increase in unwanted side-effects [17]. Children with challenging behaviors may benefit from this combination. However, very often it may be impossible to give the premedication via the oral route. Alternative routes such as intranasal, intramuscular, and submucosal routes of administration should be considered. Intranasal dose 0.2 mg/kg of midazolam provides fast onset of sedation with peak effect at 20 min. Ketamine 1–2 mg/kg administered nasally with midazolam accelerates the onset of sedation with no adverse events [18]. The intramuscular injection is rarely used and should be reserved for the most challenging behaviors, where rapid reliable delivery is required and other routes have failed [14].

Intra-operative Management

Monitoring

In addition to standard monitoring (ECG, pulse oximetry, capnometry/capnography, temperature, heart rate, respiratory rate, and noninvasive blood pressure), arterial line placement and invasive arterial blood pressure monitoring is required for orthopaedic surgery whenever massive blood loss or induced hypotension is anticipated [19]. Foley catheter placement is recommended in cases when urine output monitoring is needed for correct fluid replacements. Due to the length of many orthopaedic procedures, continuous esophageal temperature monitoring is necessary to minimize the risk of hypothermia (which can worsen coagulopathy and increase blood loss). Also, for children undergoing spinal fusion surgery, intra-operative neurophysiologic monitoring has to be establishing to protect neural tissue during instrumentation. By detecting intra-operative spinal cord compromise early, neurologic monitoring can allow surgical intervention to decrease the incidence of new-onset iatrogenic post-operative neurological deficit [20]. Somatosensory evoked potentials (SSEPs) and transcranial electric motor evoked potentials (tcMEPs) is also frequently employed, and monitors have to be placed after induction, tracheal intubation, vascular access, and positioning.

Anesthetic Management

The idea of general anesthesia for pediatric patients as a major component of anti-nociceptive protection during orthopaedic surgery is readily accepted. Regional anesthetic techniques, such as nerve plexus blocks and spinal and epidural anesthesia are starting to gain favor in the pediatric population as well. Many anesthesiologists combine regional anesthesia (caudal, epidural anesthesia with local anesthetics/clonidine mixture) with general anesthesia as a component of anti-nociceptive peri-operative protection and later in post-operative period even for ambulatory patients [21]. Induction anesthesia can be divided into two major types – rapid inhalational and rapid intravenous induction. The choice of induction technique depends on the age of the patient and his/her ability to tolerate peripheral intravenous (IV) catheter placement. For children older than 10 years, most anesthesiologists prefer peripheral IV placement and induction with propofol in dose 2.5 mg/kg, followed by maintenance with inhalational anesthetics (Isoflurane, Sevoflurane) delivered through facial mask for short procedures (arthroscopy, bones repositions, fracture reduction, etc.) with small boluses of fentanyl 1 μg/kg during the most traumatic stages of surgery. Some authors advocate propofol-ketamine 1:1 mixture bolus followed by a continuous infusion for deep sedation or general anesthesia in combination with regional anesthesia, even for prolonged orthopaedic surgery [22].

For surgical interventions that continue longer than 30 min, laryngeal mask airway (LMA) placement is frequently used. If a LMA is used, induction with propofol 2.5 mg/kg followed by administration of fentanyl bolus 2 mcg/kg will abolish upper airway reflexes and allowed positioning of the LMA without complications. After LMA

placement, maintenance anesthesia is provided with N_2O/O_2 (1:2 ratio) mixture with inhalational anesthetic in a dose adjusted to mean alveolar concentration (MAC) and fentany boluses prior to most traumatic manipulations.

If the surgery is going to be prolonged (several hours in duration) or if the patient needs to be specifically positioned with risk of airway compromise, tracheal intubation is performed. Many authors advocate rapid sequence intubation with etomidate and rocuronium, which provides effective intubating conditions characterized by a superior hemodynamic profile and rapid paralysis without any serious complications [23]. After intubation, anesthesia can be maintained with inhalational anesthetics or total intravenous anesthesia (TIVA) with propofol 100–200 μg/kg/min in combination with morphine/ fentanyl boluses or continuous remifentanyl 0.2–1.0 μg/kg/min or sufentanyl 0.25–0.5 μg/kg/h infusions. Also, TIVA for scoliosis surgery can be provided with concomitant dexmedetomidine and ketamine infusion. The dexmedetomidine dose ranges from 0.9 to 1.2 μg/kg/h and ketamine 0.4–0.6 mg/kg/h; the analgesic properties of both are complimented by the continuous fentanyl infusion at 1–2 μg/kg/h [24].

Many anesthesiologists prefer to use regional anesthesia as a component of multimodal anti-nociceptive protection in combination with general anesthesia whenever possible. The combination of thoracic epidural anesthesia (TEA) or spinal anesthesia (SA) with general anesthesia offers several advantages [25], including dramatically lower blood loss and dry surgical field as result of venous hypotension in spine secondary to sympathetic blockade, highly effective anti-nociceptive protection during the surgery, and significantly superior analgesia when using TEA with opioids, local anesthetics [26] or both in combination [27] during both the intra-operative and post-operative period (which is superior to parenteral opioid analgesia, including intravenous patient controlled analgesia (PCA) with opioids) [28, 29]. Additional advantages include accelerated recovery after surgery, significantly lower rates of nausea or vomiting in post-operative period, and earlier return of bowel function [30–34]. However, epidural or spinal anesthesia application may be technically challenging in children with scoliosis secondary to complicated spine anatomy [35]. However, in experienced hands, the success rate for thoracic epidural catheter (TEC) placement before surgery is 96.6 % [36]. For TEA during intraoperative period low concentrations of local anesthetics such as 0.125–0.2 % levobupivacain or bupivacaine, 0.1 % ropivacaine can be used alone or in combination with morphine or hydromorphone [37].

One additional point to consider is whether monitoring SSEPs and tcMEPs is going to be utilized. It is very well known that many commonly used anesthetic agents produce a dose-dependent amplitude reduction and latency prolongation of evoked response, which may impair diagnosis of diagnosis of intraoperative spinal cord injury. The volatile anesthetics halothane, enflurane, isoflurane with mean alveolar concentration (MAC) above 1.0 as well as sevoflurane, desflurane with MAC above 1.5 and lower MAC if they are combined with nitrous oxide should be avoided [38]. Nitrous oxide alone diminishes cortical SSEPs by approximately 50 % [39], potentiates the depressant effects of volatile anesthetics [40] and most intravenous anesthetics [41] and is contraindicate for SPS. Intravenous anesthetics in low doses have minimal effects on SSEPs, however, high doses of most agents cause slight to moderate decreases in amplitude and increases latency [38]. According to different authors, opioids such as morphine, fentanyl, remifentanil, and sufentanil administered in analgesic or anesthetic doses cause clinically unimportant changes in SSEPs latency and amplitude [42, 43]. Dexmedetomidine at sedative dose 0.5 μg/kg/min combined with systemically administered opioids (sufentanil, remifentanil) affects SSEPs amplitude minimally and provides good conditions for monitoring [20, 44]. Ketamine, 3 mg/kg, followed by 2 mg/kg/h combined with 0.15 mg/kg/h midazolam provides satisfactory recording during major spinal surgery even in combination with nitrous oxide [45].

Positioning

Anesthetized patients are extremely vulnerable during positioning secondary to absence of the sensation of discomfort. Especially vulnerable areas are peripheral nerves, nipples, eyes (in case of prone position), and male genitalia. All of the pressure points require adequate padding to avoid peripheral nerves compression and soft tissues damage. Positioning requires an orchestrated approach.

Visual Deficit After Prone Surgery

After prone spinal surgery, the estimates of permanent visual deficits are as high as 1 out of 1,100 [46]. The majority of the cases are attributed to ischemic optic neuropathy (ION) with posterior ischemic optic neuropathy (PION) predominating over anterior ischemic optic neuropathy (AION) [47]. A number of intra-operative factors have been proposed to be associated with peri-operative visual loss in patients undergoing spine surgery. These include hypotension (including the use of the "deliberate hypotension technique"), blood loss, anemia, hypovolemia, hypoxia, hemodilution, facial edema, pressure on the eye, use of vasopressors, prone and head-down positions, substantial fluid resuscitation, increased venous pressures, and prolonged surgery [48]. Among these factors, there are three predominant factors associated with development of visual loss – prone position, duration of surgery, and substantial blood loss [49, 50]. It was found that prone position cause increase intraocular pressure (which was result of venous congestion and increase intraorbital venous pressure), choroid layer thickness, and optic nerve diameter in prone position compared with supine

position, which increases further with time over 5 h [49]. Also, it was shown that even minimal table elevation of 4° provided a significant attenuation of one of the parameter; further table elevation to 30° slowly normalize the other parameters [49]. Systemic blood pressure must be continually monitored and use of deliberate hypotension should be determined on a case-by- cases basis with serious attention to patients with chronic arterial hypertension. The use of large volumes of crystalloids has been shown to be associated with increased intra-operative ocular pressure, periorbital edema, and double vision. For this reason, colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss [48]. In addition, direct pressure on the eye should be avoided to reduce the risk of central retinal artery occlusion and other ocular damage. The patient's head should be positioned at the level with or higher than the heart in a neutral forward position in high-risk patients; a specialized headrest such as preformed foam headrest should be used, eyes of prone-positioned patients should be regularly assessed and documented. There are no prospective studies that have determined the level of hemoglobin associated with peri-operative visual loss, however most specialists agree that the hemoglobin level should be periodically monitored during surgery in patients who experience substantial blood loss and intraoperative hemoglobin or hematocrit should be maintained at a minimum average of 9.4 g/dl or 28 % respectively [49].

Bleeding

Highly traumatic orthopaedic surgery, especially posterior scoliosis surgery is associated with considerable blood loss. The blood loss depends on several factors such as the type of surgery, severity, surgical approach, operative time and extent of intervention, and the presence of coexisting bleeding disorders (von Willebrand disease is most common). From the current literature, patients undergoing scoliosis surgery can have up to 4.5 l of blood loss [51]. These patients often require from 1 to 8 units of allogeneic red blood cells (RBC) transfusion [52]. At the same time, allogeneic transfusions are associated with several complications. The most important ones include transfusion related acute lung injury (TRALI) [53], transfusion-induced immunomodulation that is thought to contribute to the observed higher incidence of nosocomial infections in post-operative patients [54, 55], and finally, directly transmitted infections (hepatitis, human immunodeficiency virus, West Nile viruses) [56]. Such complications support the observations that transfused patients have increased resource utilization, like prolonged duration of mechanical ventilation [57, 58], longer hospital stay, and higher mortality [59, 60].

There are multiple interventions that should be used to minimize blood loss, especially for scoliosis surgery. Several of these interventions have been discussed elsewhere in this textbook (see in particular the chapter on blood conservation in the OR). These include position on spinal table to decrease abdominal pressure and venous congestion, electrocautery, and topical hemostatic agents. Also, one of the very effective and widely used approaches to minimize blood loss is hypotensive anesthesia [61]. Hypotensive anesthesia can be achieved with deep anesthesia per se or with the use of systemic vasodilators such as sodium nitroprusside or nitroglycerin. A multi-center study showed that use of antifibrinolytics (aprotinin and ε-aminocaproic acid) significantly decreases blood loss and transfusion requirements in surgical patients [62–64]. Some authors recommend tranexamic acid in loading dose 100 mg/kg given over 15 min before incision followed by an infusion of 10 mg/kg/h during surgery [65]. The use intra-operative cell savage and autologus blood transfusion has been demonstrated as a safe and effective method of reducing allogenic blood transfusion, especially for cardiac and orthopedic surgery and should be considered in all cases where significant blood loss is expected. However, when patients are autotransfused large volumes, this is often accompanied by coagulopathy, as the washing process discards all platelets and clotting factors [66]. Therefore, laboratory testing such as prothrombin time, fibrinogen, and platelets count should be carried out and blood product replacement considered.

Spinal Cord Dysfunction

Spinal cord dysfunction during scoliosis surgery most often is the result of spinal cord ischemia that by stretching or compression of vessels or interrupting blood flow to radicular arteries. To assess spinal cord function, anesthesiologists used to employ a wake-up test that has been considered "gold standard" for assessment of motor function during scoliosis surgery. The test involved awakening the patient after spinal distraction to the point that he or she could follow commands to move the hands and feet. Importantly, the wake up test only provided information regarding anterior spinal cord function (motor, corticospinal tract) but did not test the function of the dorsal column (sensory, spinothalamic tract). This approach has been largely replaced by more sophisticated electrophysiological monitoring of spinal cord function such as SSEPs and tcMEPs that provide continuous assessment functional integrity of neural pathways in anesthetized patients [20, 40].

Hypothermia

Hypothermia during orthopaedic surgery is the result of multiple factors, such as general anesthesia inhibition of central and peripheral responses of thermoregulation as well

as inhibition of heat production, heat loss secondary to large surgical incisions, and infusion of cold crystalloids and blood products. To avoid hypothermia (which can be associated with multiple complications, most important of which are electrolyte abnormalities and coagulopathy), continuous esophageal pressure monitoring is recommended. The ambient temperature in operating room should be optimized, and radiant heaters, warming blankets ("Bear huggers"), and mattresses should be used. Finally, warming intravenous fluids and blood products, humidification, and heating inspiratory gases will help to minimize heat loss.

Post-operative Management

As mentioned above, admission to the PICU following orthopaedic procedures such as spinal fusion surgery is certainly not universal and will be largely dictated by the presence of co-morbid conditions and/or technology-dependence (e.g. non-invasive or invasive positive pressure ventilator support). Post-operative management (including whether the patient is admitted to the surgical ward or PICU) depends upon many factors, including pre-operative medical problems (including co-existing disease and chronic disease), extent of surgical invasion, intraoperative course (blood loss, fluid balance, type of anesthesia, and effectiveness of perioperative anti-nociceptive protection), and effectiveness of muscle relaxant reversal [67]. Regardless, an adequate handoff between the surgical team and PICU (or ward) team is imperative. Major problems that can be anticipated in these patients include hemodynamic instability from hypovolemia or excessive blood loss; respiratory compromise due to excessive analgesia/sedation, residual neuromuscular blockade, atelectasis after prolonged general anesthesia and immobilization, TRALI, pulmonary embolism, or concomitant restrictive lung disease; pain; fluid and electrolyte imbalances; paralytic ileus; and deep venous thrombosis (DVT). With regards to fluid and electrolyte imbalances, the syndrome of inappropriate antidiuretic hormone (SIADH) occurs relatively frequently after spinal fusion surgery and can be potentially life threatening, if not readily recognized and treated in an expeditious manner [68]. Effective recognition and appropriate management of all potential complications noted above can and will improve outcomes and reduce the length of stay (LOS) in the PICU. Close communication with the surgical team is imperative.

Cardiovascular and Hemodynamic Issues

Hypovolemia is one of the most often recognized complications after major orthopaedic surgery and is the result of inadequate replacement of intra-operative fluid losses as well as fluid "third spacing". Blood loss contributes to this problem, which can usually be easily recognized by the presence of tachycardia, decreased urine output and deficient peripheral perfusion. Rehydration and replacement of ongoing fluid losses with maintenance fluid therapy and intermittent boluses of normal saline (NS), as needed is usually effective. These patients may also have a relative hypovolemia (due to vasodilation of capacitance blood vessels and a subsequent reduction in the effective mean circulatory pressure), especially when regional anesthesia/analgesia techniques have been employed. This problem is effectively managed with administration of crystalloid boluses or low dose, continuous infuions of vasoactive medications (e.g., norepinephrine, epinephrine, phenylephrine, dopamine) as well as by decreasing the doses of local anesthetics infused to epidural space.

Respiratory Issues

Respiratory insufficiency with increased oxygen (O_2) requirements can be the result of atelectasis and should be managed with O_2 supplementation and rarely with high flow or continuous positive airway pressure (CPAP). In cases, when hypoxemia co-exists with hypoventilation, opiate overdose should be suspected, especially if the patient has pin-points pupils, arterial hypotension, and a decreased response to painful stimulus. Treatment includes temporary non-invasive biphasic positive airway pressure ventilation (BiPAP) or carefully used intermittent small doses of naloxone that are just enough to reverse the opiate-induced respiratory depression (generally, the doses required to reverse opiate-induced respiratory depression are significantly less than the usual doses listed in most formularies, e.g., on the order of 5–10 μg/kg in repeat increments, titrated to effect). Additional respiratory complications include pulmonary embolus, fat embolus, TRALI (particular if the patient required multiple blood products during or immediately after surgery), or rarely, fluid overload. In these cases, invasive mechanical ventilation is required with judicious use of positive end-expiratory pressure (PEEP) and a low tidal-volume strategy (see the chapter on Mechanical Ventilation). Finally, it should be mentioned that many patients with scoliosis may have restrictive lung disease, which also impacts the post-operative course. Many children with neuromuscular scoliosis will have a history of obstructive sleep apnea or hypoventilation requiring respiratory support in the post-operative period as well.

Pain Management Issues

Aggressive surgical intervention is typically followed by acute pain. In the context of orthopaedic surgery, the pain is somatic (arising from skin, muscle, and bones). In addition to the emotional and physical suffering associated with pain,

negative effects of pain include tachycardia, hypertension, and increased O_2 consumption; impaired bowel movement; inadequate respiratory effort or "splinting" that leads to worsening atelectasis; delayed mobilization, which can increase the risk of pressure ulcers and venous thromboembolism. Also, uncontrolled severe acute pain is a risk factor for the development of chronic pain. All of the above factors emphasize the need for aggressive pain control.

Assessment of pain is a crucial element in effective post-operative pain management and should be done when the patient is at rest and moving, as well as before and after every given treatment. There are more than a few pain assessment scales (facial expression, verbal rating scale and etc.) that are used to quantify pain, however it is strongly recommended to use one scale that is "universal" within a hospital in order to ensure that everyone "speaks the same language" regarding the intensity of pain. Effective treatment options for acute post-operative pain include balanced (multimodal) analgesia as well as non-pharmacological techniques (television, music and other kind of distractions). Balanced (multimodal) analgesia means the use of two or more medications, as well as method of medications delivery (systemic, regional) that act throughout different mechanisms to achieve effective analgesia with minimization of possible adverse effects. The pharmacological options include non-opioid analgesics (paracetamol, NSAID's, gabapentin), opioids (morphine, fentanyl, codeine, etc.), ketamine, and local anesthetics with different adjuvants (clonidine, ketamine). The recommended doses for NSAIDs and non-opioid analgesics are as follows: diclofenac 1 mg/kg every 8 h oral/rectal, ibuprofen 10 mg/kg every 8 h oral, ketorolac 0.5 mg/kg every 8 h IV. The opioids doses recommended for pediatric patients: morphine 0.02–0.1 mg/kg every 6 h IV, fentanyl 2–5 mcg/kg/h continuous infusion, remifentanyl 0.05–0.1 mcg/kg/min.

Regional analgesia (epidural and spinal analgesia) or continuous central neuraxis blockade with local anesthetics and additives (opioids, ketamine, clonidine) is one of the most effective forms of post-operative analgesia and often is the number one choice for major orthopaedic surgery. Continuous epidural analgesia provides not just highly effective pain relief but also less fluctuations in pain after highly invasive orthopaedic surgeries [28]. However, important issues in pediatric regional analgesia is the appropriate site for catheter insertion. Safe catheter insertion below the first or second lumbar vertebral level may be below the desired dermatomes and may result in inadequate analgesia, therefore it is recommended to achieve catheter tip placement close to the surgical dermatome. It is possible that more hydrophilic opioids, such as hydromorphone, might result in more cephalad spread, with better analgesia in these patients; however the risk of respiratory depression with these medications is also increased [69]. The recommended doses for single epidural injection are as follows: bupivacaine 0.25 % – 1–2 mg/kg, ropivacaine 0.25 % – 1–2 mg/kg. For continuous epidural infusion: bupivacaine 0.125 % and ropivacaine 0.1 % – 0.2–0.4 mg/kg/h. Adjuvant drugs for epidural use: morphine 0.02–0.05 mg/kg, fentanyl 1–2 mcg/kg or 0.5–1 mcg/kg/h for continuous infusion, clonidine 1–2 mcg/kg, ketamine 0.5 mg/kg.

Electrolyte Abnormalities

Electrolyte abnormalities (especially hyponatremia, hypophosphatemia, and hypomagnesemia) are very common in patients following major orthopaedic surgery. SIADH is particularly common, and in the case of spinal fusion surgery results from the body's response to hypovolemia, hypotension, and dura mater traction. Hyponatremia caused by an inappropriately high level of antidiuretic hormone secretion after spinal surgery is a self-limiting phenomenon that resolves within 2 or 3 weeks. Symptoms vary depending on the severity of the hyponatremia and can range from mild headache, muscle cramps, nausea, and vomiting to convulsions, brain herniation, coma, and death. The first sign of developing SIADH is a decrease in urine output with an associated increase in urine specific gravity and increased sodium excretion with urine. During the early post-operative period after spinal fusion surgery, the patient's urine output and serum level of sodium should be monitored closely to prevent possible serious complications of the SIADH. Fluid restriction and avoiding hypotonic fluid administration (i.e. maintenance intravenous fluids should be isotonic) are generally sufficient to prevent clinically significant hyponatremia in these patients. However, hypertonic saline is indicated if the patient develops abnormal neurological symptoms.

Conclusion

Many children with orthopaedic conditions will be admitted to the PICU following surgery. Close communication with the surgical team is imperative. Early recognition and treatment of potential complications will minimize morbidity and reduce the length of stay in the hospital.

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Peri-operative Care of the ENT Patient

13

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Abstract

Peri-operative management of the pediatric ENT patient is an important aspect of pediatric critical care. This chapter discusses the pre-operative risks contributing to morbidity and mortality, intraoperative complications, and post-operative problems associated most often with the otolaryngologic diseases observed in this population. Pre-operative issues include ENT specific informed consent as well as the optimization of those underlying medical conditions which may increase the risk of complications during treatment. Clinical topics are discussed by age of presentation: birth to 1 year, toddler (1–5 years old), young children to adolescents (5 years to teenagers) and those diseases that may present in all ranges of the pediatric population. These include epiglottitis, croup, retropharyngeal abscesses, foreign body aspirations and ingestions, hemangiomas, subglottic and tracheal stenosis, tracheotomies, ENT trauma, burns, and complications of tonsillectomy and adenoidectomy. Post-operative complications may require management in the pediatric intensive care unit (PICU). Complications especially important in this population include post-operative nausea and vomiting, post-intubation respiratory compromise, pain management, and bleeding. Length of hospitalizations and readmissions in the intensive care setting for pediatric ENT patients are also discussed. The pediatric intensivist must be educated and familiar with common otolaryngologic diseases, treatment and potential complications in this age group.

Keywords

Pediatric otolaryngology • Peri-operative management • ENT • Airway anomalies

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Introduction

The peri-operative care of the pediatric ENT patient involves a multidisciplinary team of otolaryngologists, anesthesiologists, and pediatric intensivists for optimal care coordination and treatment. A thorough understanding of the pre-operative assessment, intra-operative management, and potential complications in the post-operative period is essential. Pre-operative issues include ENT specific informed consent as well as the optimization of underlying medical conditions which may increase the risk of complication during treatment. Post-operative care may require management in the pediatric intensive care unit (PICU). However, there has been a trend towards managing

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many of these conditions in the ambulatory and/or emergency department (ED) setting, resulting in a reduction in the number of patients that require hospitalization. Even fewer patients are managed in the PICU setting [1]. This is partially due to the introduction of minimally invasive surgical procedures, improved anesthetic techniques, and a push to reduce health care costs [2]. As a result, less then 1 % of ambulatory ENT procedures have significant complications requiring hospitalization. To this end, a recent study revealed the characteristics and trends of children admitted to a university affiliated PICU over the past 30 years. The number of children with epiglottis dramatically reduced from 53 patients in 1982 to 1 in the 24 month period between 2005 and 2006. The number of children with croup also decreased from 46 in 1982 to 36 in 1995 and 73 in the 24 month period between 2005 and 2006 [3]. However, there are a number of ENT diseases that do require either pre- or postoperative management in the PICU setting. These range from anatomical abnormalities diagnosed in the neonatal period to postoperative bleeding in children following tonsillectomy and adenoidectomy, which can be seen throughout all pediatric age group. Prolonged hospitalization is sometimes required due to intra- and post-operative complications, more complicated procedures, or patients with significant medical co-morbidities. The highest rate of morbidity and mortality in management of ENT procedures have been observed in patients undergoing management of diseases involving the larynx, esophagus, and trachea, with pneumonia being the most common post-operative cause of increased length of stay [2].

Pre-operative Care

There are many pre-operative management issues that are not necessarily specific to ENT that have been discussed in greater detail elsewhere in this textbook. Initially, informed consent must be obtained. As in any medical procedure or surgery, significant trust must be developed between the patient and physician. This poses a unique situation in pediatrics as consent is derived from the patient's parent or legal guardian. The ethics committee of the American Academy of Otolaryngology-Head and Neck Surgery defines informed consent as consisting of the following four elements: disclosure, comprehension, competence and voluntary choice [4]. In order to accomplish these goals, a clear description of the surgical and medical management, including the potential risks and benefits must be conveyed to the consenting parties. It has been recently shown that parents of children undergoing even the simplest otolaryngologic procedures recall only 57 % of discussed information, far less than the desired 100 %, of the surgical risks even after formal counseling prior to surgery [5]. However it is not understood why parents do not remember all the information discussed. Thus it is imperative for the surgical team to discuss peri-operative management and risks with those consenting for pediatric ENT procedures in order to ensure that all four required elements of informed consent are met. The presence of comorbid conditions in ENT patients makes this population even more predisposed to intra-operative complications, specifically relating to anesthesia. These are important for the pediatric intensivist and the pediatric anesthesiologist to understand, as complications vary between the adult and pediatric populations. For example, there is a significant increase in adverse events (4.6 % vs. 1.6 %) in patients ranging from birth to 1 year of age compared to older patients, mostly occurring during anesthesia [6]. Underlying airway and respiratory conditions, in addition to their current condition requiring surgery, are the most significant cause of complications. These include upper and lower respiratory tract infections, asthma, prematurity, history of bronchopulmonary dysplasia, and obstructive sleep apnea which can lead to bronchospasm, laryngospasm, hypoxia, and atelectasis during the procedure. These risks are increased further when there is need for tracheal intubation. Patients must be medically optimized before correction of the ENT disease to prevent unnecessary morbidity and mortality.

Care of Specific Conditions

Birth to 1 Year

Infantile Hemangiomas

Hemangiomas are the most common tumors of the pediatric population, with 50–60 % occurring in the region of the head and neck [7, 8]. The intensivist should be concerned with those involving the airway, most commonly found in the subglottic region. Although subglottic hemangiomas are the most common airway hemangioma, they only account for about 1.5 % of all congenital laryngeal lesions [9]. Infants are normally asymptomatic at birth, with symptoms occurring around 4–12 weeks of age. Known as the proliferative phase, this peaks around the age of 1 with a gradual involution period from age 2 to 5 years [10]. Presenting symptoms depend on the degree of airway obstruction, though affected infants usually present with biphasic stridor. Difficulty with feeding can also be seen with progression to retractions and further respiratory distress as the lesion enlarges. Patients are often misdiagnosed as having croup due the presenting respiratory symptoms, however patient with subglottic hemangiomas usually lack the fever that is typically present in croup. These patients are often given a course of corticosteroid therapy for the presumptive diagnosis of croup. Symptoms frequently resolve for a short period of time, as subglottic hemangiomas decreases in size due to the effects of the

corticosteroids. The intensivist should consider airway hemangiomas as an alternative diagnosis in patients that have been diagnosed with multiple episodes of croup. Patients may have subcutaneous hemangiomas elsewhere on the body, mostly on the skin. Those presenting in a "beard" distribution have an increase risk of airway involvement. Diagnosis is based on clinical symptoms with confirmation seen during endoscopy or vascular imaging studies.

The primary goal in the management of subglottic hemangioma is to maintain and secure a stable airway. Several different management options exist, including tracheotomy, external irradiation, surgical excision, laser vaporization, or corticosteroids with no present consensus or guidelines for first line therapy [11]. Depending on the severity of the presenting symptoms, it must be considered that the natural history of most hemangiomas is to spontaneously involute. In 2008 it was shown that endoscopic laser surgery had the best therapeutic outcome allowing for a secure airway with a minimally invasive technique [12]. However it was thought this also was partially due to the use of intralesional or systemic corticosteroids. Recently it has been seen that the use of propranolol as first line treatment of head and neck hemangiomas is effective, with 16/39 of patients with airway hemangiomas showing a decrease in size of the lesion [13]. Patients undergoing open excision will require admission to the PICU due to the need for postoperative intubation. This method of treatment is normally reserved for patients who do not respond to other treatment modalities. Generally, 24 h of tracheal intubation or less is required, until post-operative swelling from the procedure subsides.

Laryngotracheal Stenosis

Laryngotracheal stenosis may be seen at the supraglottic, glottis, or subglottic level. Subglottic stenosis is normally seen with other causes of laryngotracheal stenosis. These can be congenital or acquired. Congenital lesions are due to failure of the larynx to completely recanalize during intrauterine development. Acquired causes include external compression, trauma, foreign bodies, infection, inflammation, or prolonged tracheal intubation. Tracheal intubation comprises more than 90 % of acquired causes of stenosis [14, 15]. For example, patients who are tracheally intubated for 10 days or longer have as much as a 15 % increase in risk of developing stenosis. This is due to the injury sustained by the posterior glottis when the tracheal tube forces the tongue posteriorly and the posterior angulation of the trachea. These cases of stenosis are more severe and lead to greater challenges in management [16]. Gastroesophageal reflux (GERD) has been also been suggested as a cause of worsening symptoms or re-stenosis after surgery due to the tracheal aspiration of gastric contents [17]. Therefore, aggressive management of GERD in these patients is mandatory, both during the preoperative period, as well as the post-operative period.

Infants with congenital subglottic stenosis usually present within the first 2–3 months of life with biphasic stridor, often following an upper respiratory tract infection or *croup-like illness*. Even the slightest degree of inflammation and edema can precipitate partial to complete airway obstruction in these infants. Milder cases often present as recurrent croup. Tracheal stenosis is a rare cause of laryngotracheal stenosis occurring in only 0.3–1 % of all laryngotracheal stenosis [18]. Acquired laryngotracheal stenosis will present later, and there is usually a history of prolonged tracheal intubation or previous airway cannulation or manipulation. All patients suspected of having laryngotracheal stenosis need to be evaluated by endoscopy. The severity of stenosis is assessed by the ability to pass a tracheal tube through the airway using the rigid endoscope. The Myer-Cotton and McCaffrey grading systems exist to classify the degree of subglottic stenosis by determination of the size of tracheal tube that can be passed and the size and anatomical location of the stenosis respectively [19, 20].

The management of laryngotracheal stenosis is important for the intensivist since it is often a cause of severe airway compromise. Management depends upon the degree of obstruction. Patients with minor obstruction (occasional episodes of stridor, no previous hospitalizations, no feeding difficulties) can be closely observed and usually do not require prolonged hospitalization. They may require endoscopies to follow the degree of stenosis. In a large majority of these patients the stenosis will resolve spontaneously with normal growth. However, some will require surgical management. Several surgical options exist, including tracheotomy, anterior cricoid split, single stage larygotracheal resection, cricotracheal resection or stenting. Post-operative complications include change in voice, restenosis, stent dislodgement, graft displacement, or tracheomalacia. If a tracheotomy is in place, it can be decannulated after endoscopic evaluation has demonstrated a decrease in stenosis and no evidence of granulation tissue. Patients should be managed post-operatively in the PICU setting to monitor for potential airway or respiratory compromise.

Toddler: 1–5 yo

Epiglottitis

Epiglottitis is a serious, life-threatening and often fatal infection causing inflammation of the extrathoracic airway, specifically the supraglottis and epiglottis. Inflammation of the epiglottis can spread to adjacent anatomy including the vallecula and the arytenoids – for this reason, a more appropriate term to describe this condition is "supraglottitis." Supraglottitis rarely can progress to a more widespread infection and death. It is considered an otolaryngologic emergency due to the potential for sudden and complete airway obstruction.

Epiglottitis most often occurs in children age 2–8 years but is seen in all age groups, even adults. With the implementation of the Hib conjugate vaccine in 1985, the incidence dramatically decreased from 1983 to 1992 showing an incidence of 4.9 cases/100,000/year prior to introduction of the Hib vaccine to 0.02 cases/100,000/year [21]. Thus this disease is slowly changing in age of presentation from children to adults.

Infectious and non-infectious causes can lead to epiglottitis. *Haemophilus influenzae* is the most well known pathogen in the prevaccination era and is still seen today in a subset of patients even with appropriate vaccination [22]. Other causative organisms, both bacterial and viral, include but are not limited to Staphylococcus, Klebsiella, Group A β-hemolytic Streptococcus, Pseudomonas, and pneumococci [21, 23–29]. Noninfectious causes include thermal injury, trauma or inhalation leading to inflammation and edema of the epiglottis.

Presentation of a patient with epiglottitis is rapid and acute, and if not recognized and appropriately managed epiglottitis can lead to respiratory failure. Typical symptoms include fever, sore throat, dysphagia, drooling, muffled voice with no viral prodrome usually reported. These patients are toxic appearing, often assuming the tripod or "sniffing position" in an effort to maintain a patent airway. Stridor and cyanosis are symptoms of impending respiratory failure. Diagnosis is suggested from the history and physical. Once epiglottitis is suspected, a team of otolaryngologists, anesthesiologists, and pediatric intensivists should be consulted. If the patient is suitably stable, lateral neck radiographs should be obtained during inspiration with the neck hyperextended. If epiglottitis is present, it will often display the classic thumb sign – swelling of the epiglottis and thickening of the aryepiglottic folds. Obtaining and securing an airway is of utmost importance and should not be delayed, necessitating prompt admission to the PICU for closer monitoring. Patients should be kept in the sitting position or a position of maximal comfort to mitigate airway compromise. Initial management includes establishing an artificial airway using tracheal intubation, or the less desired tracheotomy. Induction is achieved by using general inhalational anesthesia of oxygen followed by increasing concentrations of Sevofluorane or Halothane. Intravenous induction agents (i.e. Propofol, Etomidate) should be not used since spontaneous ventilation is desired. The tracheal tube should be at least 0.5 mm smaller than the size that would normally be selected based upon the age of the patient. Once an airway is established, visualization of the larynx often reveals erythema and edema of all surrounding structures [30]. Cultures from tissues, secretions and blood should be obtained and the patient started on broad spectrum antibiotics against *Haemophilus influenzae* and other statistically probable organisms until culture results and sensitivities are identified. Length of tracheal intubation reports vary but can occur from 30 to 72 h. Decision to extubate is based on clinical improvement.

Foreign Body Aspiration

Aspiration and ingestion of foreign bodies is a potential cause of significant airway obstruction and respiratory compromise, with a high rate of morbidity and mortality necessitating early recognition of this diagnosis. Foreign body aspiration (FBA) presents most commonly in patients age 1–3 years of age due to the greater likelihood of this age group to place foreign objects in their mouth, immature coordination of swallowing, inadequate dentition, and decreased parental supervision with increased mobility of the child [31]. However there is a bimodal distribution with the second peak of presentation around age 10. Approximately 2.5 million US children are affected, resulting in up to 2,000 deaths per year [32]. Objects swallowed also depend on age of presentation with younger children most likely to have food products retrieved from the airway as opposed to non-organic items found in older children [33]. It has been estimated in the past that about 1 per every 110 children under the age of 14 who were treated for a choking episode actually die, thus cases of suspected FBA require timely treatment [34]. Button type batteries are particularly dangerous due to the leak of caustic chemicals and the possibility of protracted tissue necrosis. These always require emergent removal. Retrieval of these objects is of utmost importance to reduce the risk of morbidity including formation of granulation tissue, atelectasis, bronchiectasis or chronic pneumonias [35].

Children with FBA usually present with symptoms based on the location the foreign body. Although the majority lie within the right mainstem bronchus (95 %), they may also be lodged anywhere within the intra- or extrathoracic airways [36]. Symptoms may also vary based on the amount of time the object has been in the airway and the object's size. Acute aspirations often present with sudden onset of cough, wheezing, choking, stridor or respiratory distress while foreign bodies that have migrated distally over time may present with chronic pneumonias, chronic wheeze of unknown origin or may be asymptomatic. Esophageal foreign bodies though typically considered less serious than bronchial foreign bodies may present with the same symptoms and lead to airway compromise and death due to complete compression of the tracheal column.

The ability to diagnose FBs depends on their characteristics and location. However, a high degree of clinical suspicion is most important. Front and lateral plain radiographs can easily diagnose radioopaque objects, though non-radioopaque or small FBs may not be seen. Bilateral lateral decubitus films in children unable to complete both inspiratory and expiratory films may demonstrate asymmetric pulmonary aeration. Radiographic studies used to diagnose a FB only have a sensitivity of 73 % and a specificity of 45 % [37]. Patients with high clinical suspicion of foreign bodies may undergo fluoroscopic radiographs or therapeutic bronchoscopy.

Management of FBs first involves pre-operative evaluation to discuss past history of baseline lung damage from

previous injury or manipulation of the airway. Determination of active management is based on clinical symptoms and suspicion for FB. Children with mild airway obstruction may need emergent intervention, but may be closely observed if no respiratory distress is noted. Patients with threat of impending airway compromise may need to remain still or in a position of comfort to prevent migration of a partially obstructive FB. FBs must always be removed in the OR under general anesthesia secondary to possible airway compromise using a rigid bronchoscope. Spontaneous respirations are preferred because sedatives may lead to hypoxemia from decreased tone exacerbating upper airway obstruction. Intravenous atropine or glycopyrrolate may be used to dry airway secretions and for prevention of vagally induced bradycardia when the bronchoscope is inserted. There are varying theories are best anesthetic management during FB removal in the OR. Inhaled sevofluorane or an IV agent is often used for induction [38]. Sevofluorane is also preferred over halothane because it is less likely to induce coughing [39]. Propofol is often preferred because it remains at a steady state despite ventilation. Lidocaine, both topical and IV, is also used to prevent bronchospasm and coughing as well as to suppress airway reflexes during the bronchoscopy.

After the FB is removed, it is necessary to reevaluate for trauma, bleeding or granulations caused by the bronchoscope, as well as other FBs or fragments of FB that may still remain in the airway [40]. In the absence of signficant tissue trauma it is preferred to allow the patient to emerge from anesthesia without the presence of the tracheal tube due to the possibility of laryngospasm. Secretions must continually be cleared and glycopyrrolate is again often used. Intra- and post-operative complications can arise leading to possibly respiratory compromise. One must consider a pneumothorax with a sudden acute deterioration during or following the procedure. The patient may also develop hypoxia, hypotension or hypercarbia due to ventilation and anesthesia. Post operative complications that may arise include post operative wheezing in which β agonist bronchodilators are helpful, while upper airway edema and secondary stridor can be managed by racemic epinephrine or steroids. The most common post operative complication is atelectasis. Patients need close post-operative care and monitoring in the PICU in case acute intervention is needed for respiratory compromise secondary to airway edema.

Croup/Spasmodic Croup

Croup, also known as laryngotracheobronchitis is a viral illness affecting children most commonly in the toddler range. Common presenting symptoms include a viral prodrome, inspiratory stridor and a harsh barking cough [41]. Although today this is normally an easily managed and benign condition, often only requiring supportive care, historically, it was a cause of significant morbidity and mortality in the pediatric population. Due to significant advances in airway management, less than 5 % of patients require tracheal intubation. Croup is the most common cause of upper airway obstruction in the toddler population. It has a peak incidence of 2 years, with ranges from 6 months to 6 years, with rare but more serious cases occurring in the adult population [42]. It is reported that the annual incidence ranges from 1.5 to 6 % with an average of 3 % of children under the age of 6 developing croup [43]. It is most commonly seen in the fall and winter months [44]. The most common pathogen associated with croup is Parainfluenza I seen in up to 50–70 % of patients hospitalized for the disease with other pathogens including Parainfluenza II and III, influenza A and B, respiratory syncytial virus, and Mycoplasma pneumonia [42, 45].

Croup can be divided into laryngotracheobronchitis and spasmodic croup with the later being diagnosed in 3 % of the pediatric population presenting with stridor [45]. Those with spasmodic croup present with similar symptoms as those with viral laryngotracheobronchitis but without the typical fever or viral prodrome with an abrupt onset and often improvement within hours. It has been suggested that spasmodic croup differs in that it is considered an allergic reaction against viral antigens instead of being due to a viral infection [46]. Hospitalization is rarely needed and treatment as an outpatient is recommended since there is no laryngeal inflammation [47].

A typical presentation of croup includes inspiratory stridor, barking cough, hoarseness, low-grade fever and often respiratory distress. The stridor present with croup is usually inspiratory with signs of impending respiratory distress and possible failure with biphasic stridor, retractions, tachypnea, desaturations, nasal flaring and lethargy. A clinical scoring tool, the Westley uses the presence and severity of five symptoms to determine disease severity [48]. Diagnosis of croup should be made clinically from presenting symptoms with anteroposterior radiographs classically showing a "steeple sign," subglottic airway narrowing due to soft tissue edema confirming the diagnosis. Imaging is secondary to patients with impending respiratory failure requiring airway management.

Treatment of less severe symptoms is mostly supportive and can be performed at home or primary care settings. These include cool humidified air or humidified mist fever control and comfort measures. More severe cases can be managed with the previous treatments and the addition of oxygen for those patients with desaturations and racemic epinephrine, the most effective pharmacologic treatment in croup due its short onset of action. Racemic epinephrine is administered via a nebulized solution since it provides a vasoconstrictive effect to reduce airway edema. Due to its short half life, it may be administered every 1–2 h with close monitoring for the possibility of rebound airway edema. Less than 10 % of patients require hospitalization [49, 50].

Those requiring more frequent treatments are best managed in the PICU setting. Another treatment, though

controversial in its efficacy are systemic steroids due to their anti-inflammatory properties. Studies have shown various outcomes, though the most recent evidence demonstrates a dramatic decrease in need for prolonged hospitalizations or readmissions, ICU admissions, or need for an artificial airway after steroid treatment [51]. There has been a dramatic reduction in the severity of croup in the PICU with the introduction of steroid use [52]. Most recently the benefit of heliox has been shown to be comparable to racemic epinephrine, due to its ability to reduce turbulence around airway obstruction [53]. Since croup is overwhelmingly a viral process, antibiotics are not indicated.

Those patients with the most severe disease not responding to the above mentioned therapies necessitate further treatment in an ICU setting with an artificial airway. If tracheal intubation is required a smaller endotracheal tube must be used due to subglottic narrowing. In over, tracheotomy is needed for an airway. Direct microlaryngoscopy and bronchoscopy can be used in situations where the diagnosis of croup may be in question. Extubation usually occurs within several days.

Retropharyngeal Abscess

Retropharyngeal abscesses are potentially serious infections in the retropharyngeal space, which may lead to airway compromise. The development of this disease is due to the lymphatic spread of infection. It can also be due to trauma or foreign bodies. The majority of retropharyngeal abscesses occur in patients less than 6 year of age [54–58]. The most common symptoms at presentation are fever, neck pain/stiffness and preceding viral upper respiratory infection however symptoms can be very subtle. Respiratory distress and drooling are late symptoms. Retropharyngeal abscess has recently been called the "epiglottis of the new millennium" [54]. Physical exam often reveals cervical lymphadenopathy, a neck mass and limitation of neck mobility. Diagnosis is often made by lateral neck radiographs showing increased thickness of pre-vertebral soft tissue or by CT showing an abscess. CT has a sensitivity of 81 % with a specificity of 57 % in patients known to have a retropharyngeal abscess [55]. When surveyed, 72 % of otolaryngologists prefer CT as the initial diagnostic study [56]. Antibiotics are normally directed at *Staphylococcus aureus*. There is mixed opinions as proper treatment – a trial of antibiotics versus excising the abscess in the OR [57]. Patients with more complicated clinical courses (i.e. requiring more than one procedure to treat the abscess or presence of multiple abscesses) are more likely to present with airway obstruction requiring an admission to a PICU [58].

Children to Adolescents

Tonsillectomy and Adenoidectomy

Tonsillectomy, with or without adenoidectomy, is one of the most commonly performed surgeries with about 530,000 procedures performed in patients less than 15 years of age occurring every year in the Unites States [59, 60]. Indications for surgery include but are not limited to recurrent throat infections, tonsillar obstruction resulting in sleep apnea, change in voice quality, and refractory sinusitis. There currently is no consensus on a standard surgical technique for T&A [61]. Surgeons can either use cold instruments (tonsil knife), electrocautery, radiofrequency, or lasers. The choice of instrument normally is based on the surgeon's experience and preference. Briefly, the superior and inferior poles of tonsillar tissue are dissected from the underlying constrictor muscle. Peri-operative use of antibiotics has been shown to lessen the time to return to oral intake by 1 day, though the most current American Academy of Otolaryngology guideline has recommended against the routine use of antibiotics [62, 63].

Post-operative complications can be usually be classified by the time of presentation as immediate, delayed, or long-term. The intensivist should be aware of these, as patients undergoing the procedure in the current era typically have more underlying medical problems. Immediate complications occur intra-operatively or within the first 24 h post-operatively. Those which may need management in the PICU include post-obstructive pulmonary edema (POPE) and post-tonsillectomy bleeding (considered a surgical emergency). Pulmonary edema may occur after the enlarge tonsils are removed (i.e. POPE). This can cause a movement of fluid into the pulmonary interstitial due to a sudden increase in intrathoracic and hydrostatic pressure. Post-operative bleeding can be primary (occurring in the first 24 h) or secondary (in 7–10 days) post procedure [64]. It has been reported that the rate of primary hemorrhage can range up to 2.2 % and at high as 3.7 % in secondary bleeding [65]. Primary bleeding is most commonly associated with surgical technique. Secondary bleeding is most commonly caused by premature separation of the eschar. Hemorrhage can be severe enough to cause hypotension or hemorrhagic shock. Control of bleeding may require tracheal intubation, which is often in the face of active bleeding. Non-steroidal anti-inflammatory drugs (NSAIDS) are frequently prescribed for relief of post-operative pain. While NSAIDS may increase the risk of bleeding, it is generally felt that the need for effective pain management outweighs the potential risk of bleeding [66]. In 2011 the American Academy of Otolaryngology-Head and Neck Surgery proposed revised guidelines regarding the management of T&A [63].

All Ages

Inhalation Injuries/Burns and ENT Trauma

Inhalation injury and airway trauma are covered in other chapters of this textbook.

Tracheotomy

With current advances in critical care management, the incidence of pediatric tracheotomies has dramatically decreased [67]. Several indications for tracheotomy include the need for prolonged ventilation, severe neurological impairment with decreased ability to protect the airway, need for continued pulmonary toilet, pre-existing fixed airway problems, or severe airway obstruction. Rates of tracheotomy are increased in patients with underlying respiratory processes. The neurologic status of a patient most accurately predicts the need for tracheotomy [68]. It has been suggested that the period of time pediatric patients can be safely intubated ranges between 30 and 60 days, at which time a tracheotomy should be considered [69]. The risks of tracheotomy include those seen intra-operatively such as bleeding, pneumothorax and difficulties with ventilation. Post-operative complications include the inability to replace the tracheotomy tube in the event of accidental decannulation, infections of the wound and stoma, neck skin erosion, tracheotomy tube occlusion, subglottic stenosis and the development of tracheocutaneous fistula. Those patients with severe underlying medical conditions are also at risk for anesthesia related complications during the surgical procedure.

In the past, tracheotomy was performed only in the OR with general anesthesia. The current overall risk of mortality has been shown to be between 0.5 and 18 % [70, 71]. With a decreased risk of complications and the current empahsis on improving cost effective medicine, tracheotomy in the intensive care setting is increasing. With appropriate patient selection and good technique, Klotz et al. showed no deaths and a complication rate of 7 % with pediatric bedside tracheotomies, with a significant reduction in the cost of care [72].

Post-operative Care

Post-operative care of the ENT patient in the PICU requires a thorough understanding of the physiology, anatomy and pathology of pediatric otolaryngologic diseases underlying medical problems, anesthetic agents used if a surgery was performed, details of the medical and intraoperative surgical management and complications during treatment. Based on these considerations, some post-operative complications may be anticipated and prevented.

Today, the majority of ENT procedures are performed on an outpatient basis however those patients with complicated procedures or complex underlying medical conditions may need post-operative care in the PICU [1]. It has been shown that a prolonged length of stay and unplanned postoperative hospitalization in the pediatric population are usually due to respiratory complications [73]. For example, hospital acquired pneumonia has been shown to be the most common post-operative complication (3.5 %) in the ENT patient [3, 74, 75]. Pneumonia was associated with an increased length of stay from 4.7 days in patients without pneumonia to 19.7 days with pneumonia [75]. Hospital acquired pneumonia may have important implications for reimbursement from third party payers.

Complications specifically related to tracheal intubation are often increased in ENT patients. These include post-intubation croup, asthma, and pulmonary edema. The most common post-operative complication or side effect of general anesthesia is post-operative nausea and vomiting [76]. Bleeding is also a serious complication. Even with routine laboratory screening, post-operative bleeding following tonsillectomy is neither foreseeable nor preventable [77]. Lastly, post-operative pain management and sedation is also an important issue in ENT patients.

Conclusion

The peri-operative management of the ENT patient requires a multidisciplinary team in the PICU. Specific ENT diseases present in different ages from newborn to adolescents and can be congenital or acquired. Management differs in these age groups compared to adults because of their variation in anatomy. Often these diseases require surgical interventions in addition to medical treatment for improvement or resolution of the problem after which the intensive care unit needs to monitor for potential complications. Therefore the pediatric intensivist must be educated and familiar with common otolaryngologic diseases, treatment and potential complications in this age group.

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Part III

Trauma

Richard A. Falcone

Head and Neck Trauma

14

Derek S. Wheeler, Derek Andrew Bruce,
and Charles Schleien

Abstract

While the overall mortality rates have decreased significantly, TBI remains a significant public health problem. In addition, while cervical spine and spinal cord injuries are less common in children compared to adults, these injuries are an important source of long-term morbidity and pose a significant burden on the health care system. The management of these injuries has continued to evolve over time. Critically injured children with TBI require the close coordination of management between the PICU team, the trauma surgeon, and the neurosurgeon.

Keywords

Traumatic brain injury • Depressed skull fracture • Closed head injury • Cervical spine injury • SCIWORA • Spinal cord injury • Epidural hematoma • Subdural hematoma • Intracranial hypertension

Introduction

Trauma is the leading cause of pediatric morbidity and mortality in the United States. The mortality rate due to trauma has declined significantly in all age groups since 1979, largely as a result of aggressive injury prevention programs. However, accidental injury still accounts for more than one-third of all childhood deaths [1]. Many of these deaths are due to traumatic brain injury (TBI) [2]. Neck and cervical spinal cord injuries, although relatively rare in the pediatric population, often have catastrophic consequences [3–5]. Clearly, pediatric head and spinal cord trauma creates a significant burden on society.

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Head Trauma

Epidemiology

While the overall mortality rates have decreased significantly, TBI remains a significant public health problem. Seat-belt and bicycle helmet laws have resulted in a dramatic decrease in both the number and severity of TBI in children [6, 7]. Although children generally have better survival rates than adults [6], the life-long sequelae of even a mild TBI can be more devastating in children due to their young age and developmental potential [8, 9]. The usual mechanism of injury depends on the age of the patient. For example, children under 4 years most often suffer TBI secondary to falls, motor vehicle accidents, or non-accidental trauma (child abuse), while TBI in older children usually occurs second-

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ary to sporting or motor vehicle accidents. In the adolescent population, motor vehicle accidents and assault or violent crime are the most common causes of TBI [6, 9]. Males appear to sustain TBI almost twice as often as females, especially in the adolescent age group. Most large series show an increased incidence of head trauma in the spring and summer months when children are more likely to be outdoors [10]. As mentioned above, pediatric TBI is a significant burden to the health care system, accounting for more than $1 billion in total hospital charges every year in the United States alone. These costs do not take into account the costs of future medical care, years of lost work, and the years of lost quality of life, which are likely to be significantly greater [11].

Physical abuse (inflicted trauma) is the leading cause of serious head injury and death in children under 2 years of age [12]. The mechanism of injury in inflicted or abusive head trauma is controversial, but likely involves a combination of shaking, asphyxia, and blunt trauma to the head. The distinction between inflicted and accidental head injury in young children is important as it greatly affects prognosis. Outcome among children with non-accidental head trauma is significantly worse, and the majority of survivors suffer significant disability and neurologic impairment [13]. Inflicted or abusive head trauma is discussed in greater detail elsewhere in this textbook.

Pathophysiology

The pathophysiology of TBI is specific to either the primary or secondary insult. Primary injury is the injury that results directly from the original impact and is best prevented by aggressive injury prevention programs, including the proper use of safety devices such as seatbelts, bicycle helmets, and air bags. Primary head injury can involve damage to the scalp, cranial bone, dura, blood vessels, and brain tissue as a result of immediate application of acceleration/deceleration forces with or without impact. Both contact and inertial forces may be involved in the primary injury. Linear force vectors occur when the head is struck by a moving object and are responsible for generating contact force. Inertial forces are created by acceleration/deceleration or angular-rotational movement of the head in space. Because the child's head-to-torso ratio is much greater than that of the adult, inertial forces are magnified in children resulting in more diffuse brain injury. The relatively higher water content and incomplete myelination of the pediatric brain may also contribute to the diffuse nature of the injury in the immature brain as compared to the more focal adult pattern [14].

Impact injuries to a static head have their greatest effects on the skin and skull and, as a result of absorption of the force by these tissues, less effect on the brain tissue and brain blood vessels. For example, children with depressed skull fractures may have an associated cerebral contusion, though the predominant damage occurs to the skull. Acceleration/deceleration forces, whether associated with impact or not, result in complex deformations of the brain and its blood vessels that can lead to a variety of pathologies from (i) shearing injury of the white matter, with or without hemorrhage, (ii) contusion or laceration of the cortex or deep structures, including the midbrain and medulla, (iii) disruption of arteries or veins with subsequent hemorrhage, and (iv) disruption of the blood-brain barrier.

Secondary brain injury results from the physiologic and biochemical events that occur after the initial trauma or primary brain injury. The best recognized of these secondary injuries are systemic hypotension, hypoxemia, hypercarbia, intracranial hypertension, and cerebrovascular spasm. Hypotension and hypoxia commonly present on admission to the emergency department (ED) and thus any secondary damage may already have been sustained prior to advanced medical care (i.e., in the ED or PICU). However, intracranial hypertension tends to progress over several days and is rarely present during the early stages after initial resuscitation.

Other secondary injuries may be produced by a variety of molecular events (discussed elsewhere in this textbook in much greater detail) such as the release of excitotoxic neurotransmitters or free oxygen radicals. Multiple mechanisms have been implicated in secondary brain injury and include cerebral ischemia, release of excitatory neurotransmitters, free radical formation, activation of neuronal apoptosis cascades, and blood-brain barrier disruption leading to cerebral edema. The role of these mechanisms in human brain trauma is unclear and no specific therapies are available to correct or modify these molecular events.

In children, cerebral blood flow (CBF) is reduced shortly after TBI. Loss of endogenous vasodilators such as nitric oxide and elaboration of vasoconstrictors such as endothelin-1 have been implicated in producing post-traumatic hypoperfusion. Glutamate levels in cerebrospinal fluid have been shown to increase in humans after brain injury leading to excitotoxic neuronal death in cell culture. Glutamate exposure leads to elevation of intracellular calcium, oxidative stress, and production of free radicals. Although a portion of cell death occurs immediately after the initial insult, some neurons have been shown to die in a delayed manner by apoptosis [15]. The immature brain may be more vulnerable to apoptosis as demonstrated in experimental animal models where the severity of neurodegeneration after trauma was highest in the youngest animals [16]. Finally, both osmolar swelling in contusions and astrocyte swelling as a result of excitotoxicity contribute to significant cerebral swelling. This swelling can lead to secondary ischemia and/or herniation with their devastating consequences.

Post-traumatic insults such as hypoxia and systemic hypotension are common in children and are known to exacerbate the severity of secondary injury and worsen

prognosis [17–19]. Since intracranial hypertension, hypoxia, and systemic hypotension are the leading factors associated with poor outcome, post-injury interventions which decrease or ameliorate these events reduce secondary injury to the injured but still viable brain.

Trauma Systems

The influence of trauma systems and pediatric trauma centers on outcomes of TBI has recently been studied. Children with severe TBI are more likely to survive if treated in a pediatric trauma center or an adult trauma center with added qualifications to treat children [20–24]. Based on the wealth of experience, pediatric patients in a metropolitan area with severe TBI should be transported directly to a pediatric trauma center which will most likely be in close proximity to the accident site [25, 26]. However, for those children injured in rural areas, stabilization at an outside hospital may be indicated prior to transfer to the trauma center.

Initial Resuscitation

Immediate attention to airway, breathing, and circulation is mandatory for all unconscious children. The initial resuscitation of a child with TBI is vitally important since post-injury hypoxia and systemic hypotension are associated with worse outcome (as discussed above). It may be possible to minimize the rate of occurrence of these events with proper early resuscitation measures. Generally all resuscitation interventions are aimed at lowering intracranial pressure (ICP) and maximizing cerebral perfusion pressure and delivery of oxygen and substrate to the brain. Providing the injured brain with adequate substrate to maintain normal function is dependent on maintaining a stable airway, adequate ventilation, cardiac function, and systemic perfusion (i.e., *airway*, *breathing*, *circulation*).

Hypotension, defined as systolic blood pressure less than 5th percentile for age, has been associated with a 61 % mortality rate in children with severe TBI and an 85 % mortality rate when combined with hypoxia [27]. Hypotension has repeatedly been shown to worsen the prognosis for all levels of severity (as determined by the Glasgow Coma Score, GCS) of central nervous system (CNS) injury in children as well as in adults [17–19, 27–32]. Hypotension is present at admission in 20–30 % of severe head injuries and the avoidance of hypotension, if possible is dependent on timely recognition and resuscitation prior to arrival to the hospital. Episodes of hypotension can also occur in the hospital, both in the ED and in the PICU. The origin of these episodes is unclear and therefore avoiding them may be difficult. However, close, intensive multimodality monitoring will identify these episodes early and allow for timely intervention. While hypotension must always trigger a careful exploration for possible areas of blood loss, it can occur with isolated head injury or spinal cord injury [33].

Regardless of the etiology, hypotension must be aggressively treated. TBI can be associated with loss of normal cerebral autoregulation (Fig. 14.1), such that rapid decreases in mean arterial pressure (MAP) result in profound decreases in cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). Since children will often maintain their systolic blood pressure despite significant blood loss until they enter the later stages of hypovolemic shock, clinical signs of shock (such as tachycardia, diminished central pulses, urine output less than 1 mL/kg/h, cool extremities, and prolonged capillary refill) should be treated as if hypotension were already present and rapidly corrected with volume resuscitation. Fluid restriction to avoid exacerbating cerebral edema is contraindicated in the management of the child with TBI in shock. The use of hypertonic saline as a resuscitation fluid is gaining popularity because of the beneficial effects on ICP, though there are no clinical trials to support this type of fluid over other available agents for fluid resuscitation.

Transfusion of packed red blood cells is indicated to replace active blood loss, though the ideal transfusion trigger for critically injured children with TBI is not known [34–36]. Severe anemia is potentially harmful in patients with TBI. Furthermore, transfusion can help maintain intravascular volume and maximize oxygen carrying capacity. However, observational and retrospective studies have shown that transfusion does not necessarily improve short- and long-term outcomes [37–39]. Regardless, once the volume deficit has been corrected, a vasopressor (e.g., dopamine, epinephrine) should be administered to patients with persistent hypotension. Resuscitation fluid should be isotonic to avoid the risk of worsening cerebral edema. It is recommended that intravenous glucose be avoided in the first 48 h after injury as hyperglycemia has been associated with worse outcome [40]. However blood glucose should be monitored frequently, especially in younger children who are most at risk for hypoglycemia.

The deleterious effects of hypoxia are less well established (compared to hypotension), though there is evidence to suggest that post-injury hypoxemia, defined as PaO_2 <60–65 mmHg or oxygen saturation <90 %, portends a worse neurologic outcome in both pediatric and adult TBI patients [27, 28] and that it is a common occurrence in children with severe head injury, present in up to 45 % of patients [41]. Hypoxemia must be avoided and corrected with the use of 100 % supplemental oxygen. Although there is no evidence to support that tracheal intubation provides an advantage over bag-valve-mask ventilation in children with TBI, the current recommendation is that

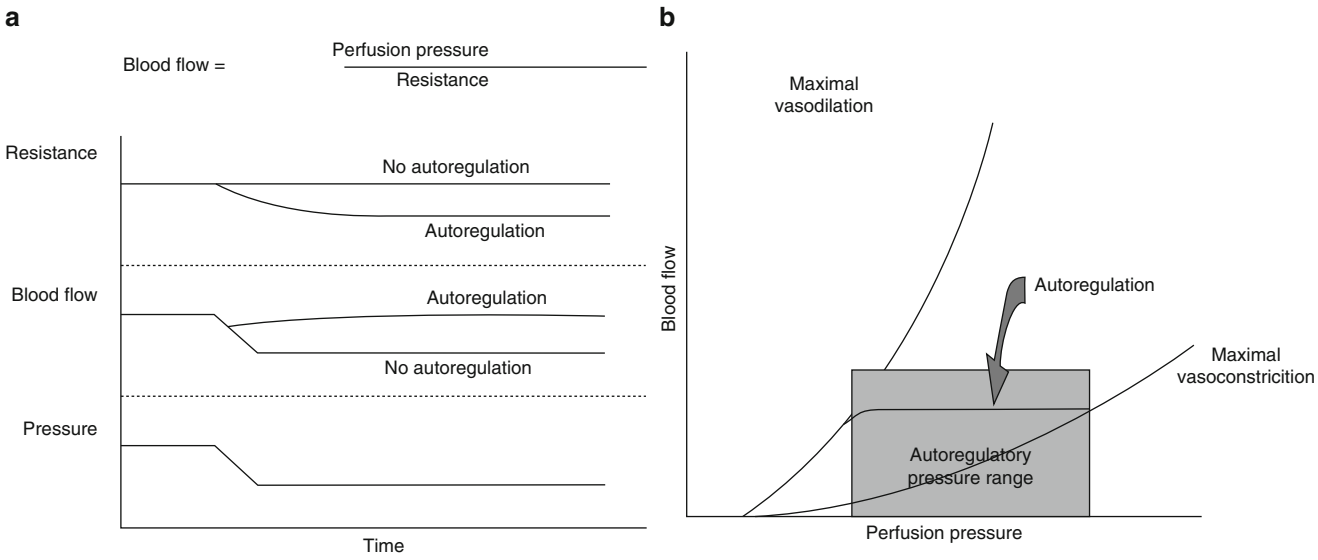

Fig. 14.1 Cerebral Blood Flow (CBF) autoregulation. (**a**) Autoregulation is the intrinsic ability of an organ, independent of neural and humoral influences, to maintain a constant blood flow despite changes in perfusion pressure. To maintain constancy in organ blood flow, as perfusion pressure is altered there must be a responsive reciprocal change in vascular resistance, mediated by a change in arterial diameter. For example, a decrease in organ blood flow resulting from a decrease in the perfusion pressure triggers a reflex autoregulatory vasodilation and reduction in vascular resistance, reconciling a return of arterial blood flow to steady state. (**b**) Maintenance of organ blood flow at a constant rate is limited by the ability of the vasculature to vasodilate and vasoconstrict. As organ perfusion pressure decreases there is a compensatory vasodilation to maintain constancy of organ blood flow. As the point of maximal vasodilation is reached, further decreases in organ perfusion pressure result in an uncompensated decrease in organ blood flow. Similarly, as organ perfusion pressure increases, there is a compensatory vasoconstriction to maintain constancy of organ blood flow. As the point of maximal vasoconstriction is reached, further increases in organ perfusion pressure result in an uncompensated increase in organ blood flow

Table 14.1 Indications for tracheal intubation in children with TBI

GCS ≤8
Decrease in GCS of >3 (independent of the initial GCS)
Anisocoria >1 mm
Apnea, bradypnea, irregular respirations
Loss of gag/cough reflex
Cervical spine injury with respiratory compromise
Inadequate oxygenation or ventilation

children with a GCS ≤8 should have their airway secured by tracheal intubation to avoid hypoxemia, hypercarbia, and aspiration (Table 14.1). Ideally, this should be performed by an individual with specialized training in the pediatric airway and with the use of capnometry/capnography to verify proper placement of the airway in the trachea (please see the chapters on Airway Management for a more in-depth discussion of this topic). These specifications are made for children because success rates of prehospital tracheal intubation in children have been shown to be lower than in adults. The cervical spine must be stabilized in the midline during tracheal intubation in any child with suspected cervical spine injury.

Children with TBI should be ventilated with the goal of maintaining $PaCO_2$ in the normal range. Aggressive hyperventilation to acutely reduce $PaCO_2$ should be reserved for the acute situation when signs of impending brain herniation are present. Chronic hyperventilation can lead to reactive vasoconstriction resulting in decreased cerebral blood flow, cerebral hypoperfusion, decreased oxygen delivery, and possibly, ischemia. Conversely, hypercarbia may lead to cerebral vasodilation which can acutely raise ICP. Most unconscious head injured children do not have intracranial hypertension upon initial presentation. Therefore, usually there is no reason to routinely administer hyperosmolar agents such as mannitol or hypertonic saline as part of the initial resuscitation. Indeed between 30 and 50 % of children with severe head injuries (depending on the study population) will not develop significant intracranial hypertension at any time during their hospital course [42–45].

As soon as the child is stable and has had a complete physical examination (including neurologic examination), the next step in management is to obtain an imaging study. Initial plain radiographs should include a lateral cervical spine, anteroposterior (AP) chest, and AP pelvis radiograph (so-called *trauma X-ray panel*). The imaging study of choice for the CNS in most centers is still a noncontrast CT scan of the head with bone windows. In addition, as most major trauma centers now have spiral CT scanners, it is relatively easy to obtain images of the spinal column, as the clinical history and exam dictate, without unnecessary delay. There is no question that MRI offers superior definition of the extent of tissue injury compared to CT, though

CT is still better at defining the extent of bony injury. However, until faster MRI scanners become available and more MRI compatible equipment is developed, CT remains the initial imaging study of choice [46]. The results of this initial CT dictate the next steps in management. If there is a significant mass lesion (e.g., epidural hematoma), surgery is usually required. However, if there is no mass lesion, the CT scan is further examined for evidence of diffuse axonal injury, ischemic injury, or signs of brain swelling (either focal or generalized). Imaging studies of other organ systems may dictate the need for surgery as well, e.g. intestinal rupture. If surgery is necessary on other organ systems in a child with a GCS ≤8, insertion of an ICP monitor at the commencement of the operative procedure is indicated, as ICP monitoring allows the anesthesiologist to monitor ICP and to control it until surgery on these other organ systems is completed.

ICP Monitoring

No randomized controlled trials evaluating the effect on outcome of severe TBI with or without ICP monitoring have been conducted in any age group. However, ICP-focused intensive management protocols have almost certainly improved outcomes [26, 47, 48]. Given the paucity of pediatric data, the current recommendations for pediatric ICP monitoring are largely based upon anecdotal experience and adult studies. Indeed, the current pediatric guidelines [26] do not make any firm recommendations and suggest that ICP monitoring may be considered for critically injured children with severe TBI (generally defined as GCS ≤8). This recommendation applies to infants as well since the presence of open fontanels and/or sutures does not negate the risk of developing intracranial hypertension nor does it alter the utility of ICP monitoring. Although ICP monitoring is not routinely recommended for infants and children with less severe injury (GCS ≥8), it may be considered in certain conscious patients with traumatic mass lesions or for patients whose neurologic status may be difficult to assess serially because of sedation or neuromuscular blockade, especially when going to the operating room for general anesthesia.

Once the decision is made to invasively monitor a patient's ICP, there are several types of monitoring devices that can be used. These are discussed elsewhere in this textbook. The ventricular catheter has been shown to be an accurate way of monitoring ICP and has the added advantage of enabling cerebrospinal fluid (CSF) drainage, making it the preferred method. Intraparenchymal monitoring devices are used commonly but have the potential for measurement drift and do not allow for CSF drainage. Morbidities related to all of these catheters, including infection, hemorrhage, and seizure are unusual.

Intracranial Hypertension

Intracranial pressure, or the pressure within the intracranial vault, is determined by the interactions between the brain parenchyma, the cerebrospinal fluid (CSF), and the cerebral blood volume. The fundamental principles of intracranial hypertension were proposed by the two Scottish physicians Monro and Kellie in 1783 [49] and 1824 [50], respectively, who stated that (i) the brain is enclosed in a non-expandable, relatively rigid space; (ii) the brain parenchyma is essentially non-compressible; (iii) the volume of blood within the skull is nearly constant; and (iv) a continuous outflow of venous blood is required to match the continuous inflow of arterial blood. However, as originally proposed, the Monro-Kellie doctrine did not take into account the volume of the CSF. As we now know, reciprocal volume changes of the CSF compartment is an important compensatory mechanism that will allow reciprocal changes in the volumes of the other cranial compartments (i.e., blood, brain) [51]. The combined volume of all of the components of the skull cavity (brain, blood, CSF) must remain constant because they are encased in a fixed volume. Therefore, if the volume of one intracranial element increases, the volume of another (e.g. CSF) must decrease to compensate and keep ICP in the normal range. ICP is therefore a reflection of the relative compliance of the cranial compartments (Fig. 14.2). As shown in Fig. 14.3, ICP will remain normal in spite of small additions of extra volume, whether edema, tumor, hematoma, etc. However, once a critical point is reached, at which compensatory mechanisms are maximized, addition of subsequent volume produces a dramatic rise in ICP.

During the initial hours following head injury, there is a diminished volume of intracranial CSF as a result of displacement of CSF into the spinal subarachnoid space, as well as increased reabsorption of brain CSF by the choroid plexus. Intracranial pressure therefore remains in a safe, normal range. However, as edema worsens or hemorrhage increases in size, these compensatory mechanisms eventually fail and ICP increases. If cerebral herniation occurs at the foramen magnum or the tentorium (Fig. 14.4), the normal CSF pathways are blocked and displacement of CSF cannot occur, resulting in a further decrease in intracranial compliance and worsening intracranial hypertension.

The perfusion of the brain, like all organs, is determined by the difference between the upstream and downstream blood pressures (i.e. perfusion pressure). The driving force for blood flow to the brain (upstream pressure) is the mean arterial pressure (MAP) and the downstream pressure, under normal physiologic circumstances, is the central venous pressure (CVP). In the case of intracranial hypertension, when the ICP exceeds the CVP, the cerebral perfusion pressure (CPP) becomes: CPP = MAP – ICP. Therefore, in order to maximize cerebral blood flow (CBF) after TBI, therapies

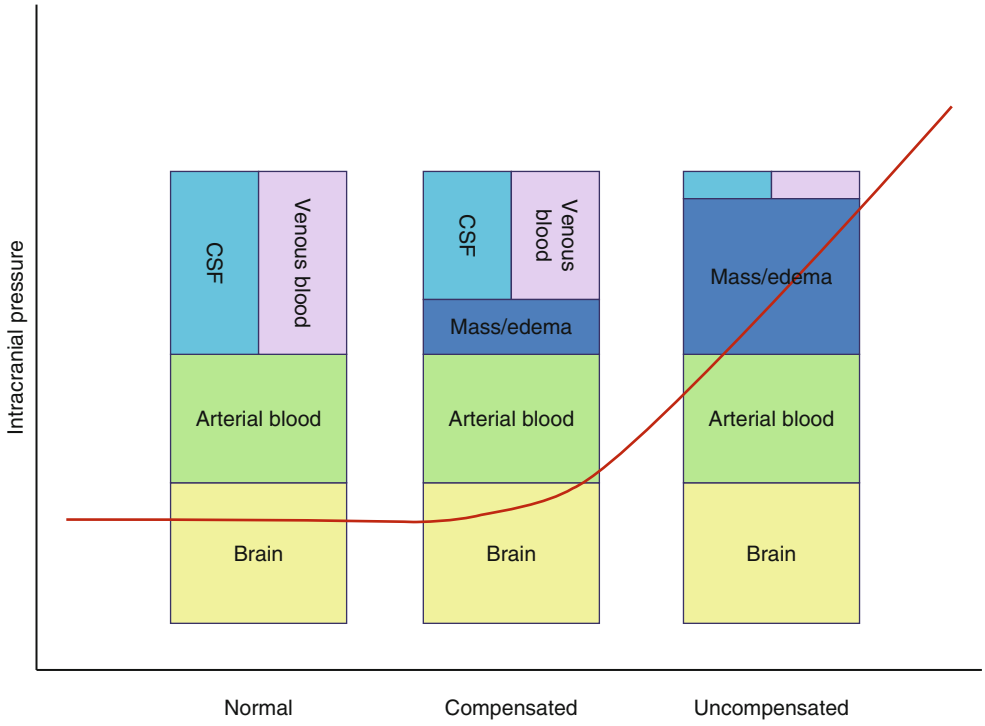

Fig. 14.2 The Monro-Kellie Doctrine. See text for detailed explanation

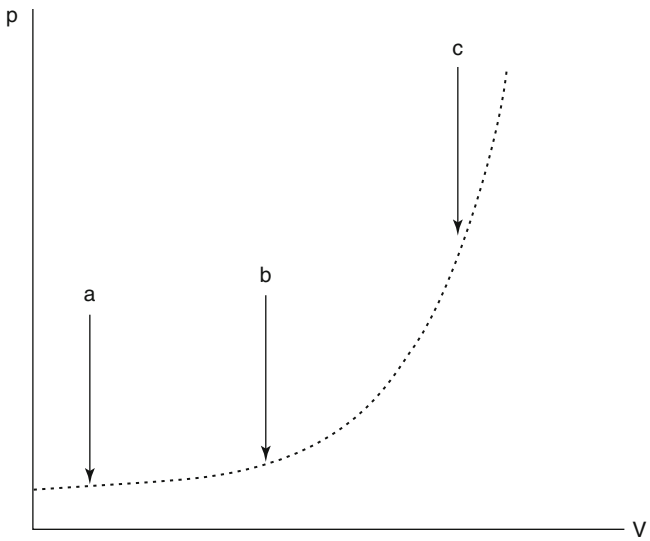

Fig. 14.3 Pressure-volume curve of the craniospinal compartment. This figure illustrates the principle that in the physiological range, i.e. near the origin of the x-axis on the graph (*point a*), intracranial pressure remains normal in spite of small additions of volume until a point of decompensation (*point b*), after which each subsequent increment in total volume results in an ever larger increment in intracranial pressure (*point c*) (Reprinted from Andrews and Citerio [51]. With permission from Springer Science + Business Media)

must be targeted to optimize MAP and reduce ICP thereby decreasing the risk of secondary brain injury. It is well known that intracranial hypertension is associated with poor neurologic outcome and that aggressive treatment of elevated ICP is associated with the best clinical outcomes.

As stated above, approximately 30–50 % of head injuries will demonstrate normal to minimally elevated ICP in the face of adequate CPP and do not require any specific therapy directed to the cranial injury [42–45, 52]. Management of these patients is therefore directed towards maintaining cardiorespiratory and hemodynamic stability. The current pediatric guidelines state that treatment efforts directed towards intracranial hypertension may be considered when ICP >20 mmHg. Similarly, the Brain Trauma Foundation and the European Brain Injury Consortium guidelines also recommend initiating treatment of intracranial hypertension if ICP ≥20 mmHg to maintain CPP in the range of 50–70 mmHg [53–55]. Two quite different approaches have been proposed for the treatment of intracranial hypertension to prevent secondary cerebral ischemia. One approach (presented above) focuses on maintaining the CPP = MAP – ICP in an acceptable range (i.e. CPP is increased by either reducing ICP, increasing MAP, or a combination of both) [56–62], while the other approach focuses on decreasing the end capillary pressure in the brain and thus reducing brain edema by slightly lowering arterial pressure and controlling end-capillary pressure and colloid osmotic pressure (the so-called *Lund concept*) [63–66]. Most intensive care units use a combination of these therapies [67, 68]. Both methods have their (at times passionate) proponents. However, there is insufficient evidence to support one method over the other at this time [69–72].

In a single-center observational study comparing ICP and survival, of the 51 children with severe closed head injury who underwent ICP monitoring, 94 % of the children in

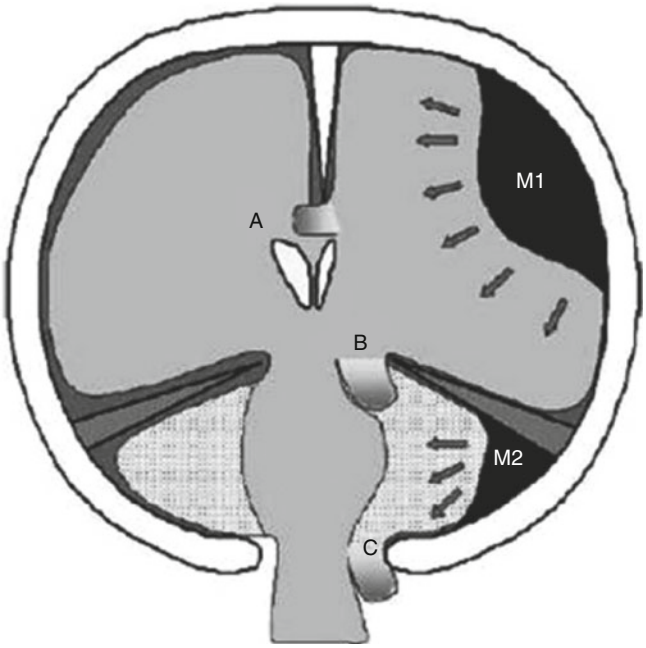

Fig. 14.4 Schematic representation of herniation syndromes. According to the Monro and Kellie doctrine, increased volume and pressure in one compartment of the brain may cause shift of brain tissue to a compartment in which the pressure is lower. M1 is an expanding supratentorial lesion; M2 is an expanding mass in the posterior fossa. A Increased pressure on one side of the brain may cause tissue to push against and slip under the falx cerebri toward the other side of the brain, B Uncal (lateral transtentorial) herniation. Increased ICP from a lateral lesion pushes tissue downward, initially compressing third cranial nerve and, subsequently, ascending reticular activating system, leading to coma, C Infratentorial herniation. Downward displacement of cerebellar tissue through the foramen magnum producing medullar compression and coma (Reprinted from Citerio and Andrews [205]. With permission from Springer Science + Business Media)

whom the ICP never exceeded 20 mmHg survived. This is in sharp contrast to the 59 % survival rate in the children with maximum ICP's greater than 20 mmHg [73]. An elevation of ICP for greater than 1 hour was found to be most deleterious and was associated with worse clinical outcome. This study, and others of its kind have led to the recommendation that treatment for intracranial hypertension should begin at an ICP of 20 mmHg or greater. Maintenance of adequate CPP is important in order to allow for ongoing delivery of metabolic substrates to the brain. Again, there are insufficient data to establish firm, consensus recommendations [26], though a minimal CPP of 40–50 mmHg may be considered for children. The pediatric consensus guidelines further suggested that the appropriate CPP may be age-based – the lower end of the aforementioned threshold is considered appropriate for infants while the upper end is considered appropriate for adolescents. A stepwise approach to the management of ICP and CPP was proposed in the original pediatric consensus guideline [25], which is still useful. Here we will present a very brief overview of the current pediatric consensus guidelines [26]. For additional discussion and a detailed reference list of supportive evidence, the reader is referred to these guidelines and the chapter on Intracranial Hypertension in this textbook.

Sedation, Analgesia and Neuromuscular Blockade

The use of sedatives and analgesics in the setting of raised ICP remains a difficult challenge. Pain and stress are known to increase cerebral metabolic demands as well as cause intracranial hypertension. However, most sedatives cause a reduction of mean arterial pressure which can decrease CPP. Additionally, these medications may exacerbate an elevated ICP by causing cerebral vasodilation, which in turn increases cerebral blood volume. Long-acting sedatives also may interfere with the ability to follow serial neurologic exams. For these reasons, short-acting agents like midazolam are preferred. Narcotics such as morphine or fentanyl can be used for pain control. Medications known to raise ICP, for example ketamine, should be avoided.

Neuromuscular blocking agents may be used to reduce ICP by preventing shivering, posturing, and breathing against the ventilator (dysynchrony). Potential harmful effects include masking of seizure activity and increased infection risk. Therefore, these agents should be reserved for specific indications and only with continuous EEG monitoring. In addition, positioning the patient with the head elevated to 30° in a midline, neutral position will facilitate adequate venous drainage through the jugular veins, helping to reduce ICP.

CSF Drainage

CSF drainage can be used as a means of controlling ICP if a ventriculostomy catheter is in place. A lumbar drain may be considered as an option for refractory intracranial hypertension if a functioning ventriculostomy is already present. Since the lateral ventricles are often small in brain injured patients and up to 30 % of the compliance of the CSF system is in the spinal axis, lumbar drains have been studied as an alternate way of diverting CSF and lowering ICP. In a retrospective analysis of 16 pediatric patients, Levy et al. reported a decrease in ICP in 14 of 16 children and improved survival after placement of a lumbar drain [74].

Hyperosmolar Therapy

Osmotic diuretics, such as mannitol, have been used extensively in the management of intracranial hypertension. Mannitol (0.25–1 g/kg IV) is effective in lowering ICP both by decreasing blood viscosity and thereby decreasing cerebral blood volume, and by gradually drawing water from the brain parenchyma into the intravascular space. This effect however requires an intact blood-brain barrier which may not be present in injured areas of the brain. Mannitol may therefore leak into the injured area and accumulate, exacerbating

focal edema. Other risks of mannitol use include acute tubular necrosis and renal failure, perhaps related to hypovolemia and dehydration. Care should be taken to maintain euvolemia and serum osmolarity below 320 mOsm/L. Hypertonic, 3 % saline is effective in controlling ICP with few adverse effects at doses of 0.1–1.0 mL/kg/h. The current consensus pediatric guidelines favor hypertonic saline over mannitol at doses between 6.5 and 10 mL/kg for acute increases in ICP [26]. A continuous infusion is an acceptable alternative. It appears that hypertonic saline can be safely used up to a serum osmolarity of 360 mOsm/L.

Hyperventilation

Prophylactic hyperventilation is contraindicated in the setting of pediatric TBI. Hypocapnia induces cerebral vasoconstriction and leads to a reduction in cerebral blood volume and ICP. Chronic hyperventilation depletes the brain's interstitial bicarbonate buffering capacity and causes a shift in the hemoglobin-oxygen dissociation curve, impairing oxygen delivery to brain tissue. In a prospective trial of severely brain injured adults randomized to prophylactic hyperventilation or normocapnic treatment, the patients in the hyperventilation group had a significantly worse outcome [75]. However, based upon the lack of definitive evidence, the current consensus guidelines recommend against prophylactic severe hypoventilation [26] and further suggest that mild hyperventilation ($PaCO_2$ 30–35 mmHg) may be considered for intracranial hypertension refractory to sedation, CSF drainage, and hyperosmolar therapy, only if advanced neuromonitoring methods are used to avoid cerebral ischemia.

Temperature Control

Hyperthermia after TBI has been correlated with worse injury and functional outcome in both animal models and clinical studies in adults. The mechanisms of damage include worsening of the secondary insult by increasing cerebral metabolic demands, damage by excitotoxicity, and cell death by stimulation of apoptotic pathways. Therefore hyperthermia should be aggressively avoided in children with TBI. The basis for the use of hypothermia (core body temperature <35 °C) in children is derived from several adult studies which show a strong correlation between hypothermia and reduced ICP with a trend towards improved outcome at 3 and 6 months after injury in a younger adult group [76]. The presumed mechanism of neuroprotection involves a decrease in excitatory amino acid release, preservation of anti-oxidants, a decrease in the release of free radicals, and anti-inflammatory effects. Although there are no clinical trials in children that show a positive effect, the current recommendation [26] is that moderate hypothermia (32–33 °C) should be considered as a treatment for intracranial hypertension in children after severe TBI, beginning within 8 h of the initial injury. If hypothermia is used, rewarming should commence at 48 h and at a rate no greater than 0.5 °C/h [26]. These new recommendations are based upon two randomized, controlled trials in critically ill children which suggested that moderate hypothermia reduced ICP. However, there was no difference in mortality or long-term outcomes in these two trials (indeed, there was a trend towards increased morbidity and mortality in the hypothermia group in the trial by Hutchison and colleagues) [77, 78].

Barbiturates

High-dose barbiturates decrease ICP by several mechanisms. They lower both resting cerebral metabolic rate and cerebral blood volume. In addition, they appear to have direct neuroprotective effects by inhibiting free radical–mediated lipid peroxidation of membranes [79]. Potential risks include myocardial depression, risk of hypotension, and the need for hemodynamic support. Barbiturates may be used for refractory intracranial hypertension in hemodynamically stable patients [80]. Starting at lower doses and titrating up to burst suppression on EEG may decrease the risk of coma-induced complications [26]. Invasive hemodynamic monitoring is frequently necessary.

Decompressive Craniectomy

Decompressive craniectomy has been shown to be an effective method of lowering ICP in children with severe head injury in several small studies. Taylor et al. reported lowered mean ICP after surgery in children with intracranial hypertension refractory to medical management and CSF drainage [81]. In addition, several case-control studies have suggested improved outcome in children undergoing early craniectomy versus a non-surgical control group [82]. The current literature suggests that decompressive craniectomy is most appropriate as a means of lowering ICP and maximizing CPP if performed within 48 h of injury in patients with diffuse cerebral swelling on CT scan, with an evolving cerebral herniation syndrome or those with secondary clinical deterioration. There have been reports of exacerbation of cerebral edema and hemorrhage after surgery and reports of poor outcome especially after non-accidental trauma [83]. Of interest, a prospective, randomized, controlled trial of early decompressive craniectomy in critically ill adults with severe traumatic brain injury showed that decompressive craniectomy decreased ICP and ICU length of stay, but was associated with more unfavorable outcomes [84]. The current pediatric consensus guidelines suggest that early decompressive craniectomy can be considered for patients with refractory intracranial hypertension [26].

Corticosteroids

Corticosteroids are not recommended in the treatment of raised ICP after pediatric TBI [26]. Multiple prospective, randomized studies failed to show improvement in ICP

management or functional outcomes with the use of steroids, and an increase in infection rate and suppression of endogenous cortisol have been observed.

Anti-convulsants

Children with severe brain injury, especially infants and toddlers, are at high risk for post-traumatic seizures in the period immediately following injury. Approximately 20 % of children will have at least one seizure following moderate to severe TBI [85–88]. Seizures increase ICP by increasing cerebral metabolic demand and causing the release of excitatory amino acids. In adults, the benefit of giving 1–2 weeks of prophylactic phenytoin has been shown to outweigh the risk. In a retrospective review of 194 children with TBI, there was a significant reduction in posttraumatic seizures in children treated with phenytoin [85]. Phenobarbital has been used for prophylaxis for infants. There is no evidence to support the use of prophylactic anti-epileptics in children or adults beyond the first 2 weeks after trauma. The pediatric consensus guidelines only state that seizure prophylaxis with phenytoin may be considered [26]. Levetiracetam may be an acceptable alternative for seizure prophylaxis [88, 89].

Surgical Management

Approximately one-third of severely head injured children have surgically treatable lesions. It is important to identify these lesions early since they can be the cause of delayed deterioration and death. However, for the majority of children with TBI, therapy is directed to maintenance of normal systemic parameters and prevention or treatment of elevated ICP.

Linear Skull Fractures

Linear fractures, which are generally the most frequently encountered type of skull fracture in children, do not require surgery. However, in a small percentage of infants and toddlers under 2 years of age, the fracture is associated with laceration of the dura and contusion of the underlying brain. The brain and CSF can insinuate themselves into the fracture and with the pulsating of the brain produce widening of the fracture edges (i.e., "growing fracture") and reabsorbtion of bone, leading to a growing skull fracture or leptomeningeal cyst. This requires surgical correction once it is clear that the fracture line is widening. Soft tissue swelling is usually palpable over the fracture site [90, 91].

Depressed Skull Fractures

In the unconscious child, closed depressed skull fractures rarely require emergency surgical correction. Many smaller lesions, especially those in the parietal region never warrant surgical elevation. The general rule is that if the fracture is depressed more than the thickness of the skull, surgical elevation of the depressed fracture should be considered. The surgical correction can be performed after the child has recovered from coma. There is no evidence that the surgery has any beneficial effect on long-term outcome other than improving appearance [92, 93].

Compound Skull Fractures

Since compound skull fractures are by definition open wounds, they are associated with a high risk for infection of the skull or brain. Early operation, within the first 12 h to debride the brain, close the dura, and reconstruct the skull is widely accepted. In most cases the broken pieces of bone can be sterilized and replaced to achieve an immediate reconstruction of the skull. Removal of all intracerebral bone debris is important for avoiding delayed abscess formation [92]. Delayed surgical correction has been proposed in those children who require intensive management of intracranial hypertension [94].

Fractures that involve the anterior skull base with brain extruding into the ethmoid sinus can pose a logistic problem. These are usually associated with frontal bone fractures and, in older children, facial fractures [95]. If there is brain swelling it can be difficult to get adequate exposure of the anterior skull base to assure a good reconstruction and therefore the surgery may have to be delayed until the life-threatening increases in ICP are controlled. If the child is evaluated early before significant intracranial swelling has occurred, both the skull base and facial fractures can be repaired in a single operation. The advantage is the prevention of increased cerebral herniation through the fracture site during the period of brain swelling (and the attendant risk of formation of leptomeningeal cysts). Finally, prophylactic antibiotics are not generally indicated in the management of skull fractures, except in the case of compound skull fractures. However, tetanus toxoid and tetanus vaccination booster should be administered if the vaccination status is not up to date.

Epidural Hematomas

Epidural hematomas occur in 3–8 % of children hospitalized after head injury [96]. Most epidural hematomas are the result of falls, automobile or bicycle accidents, or skate boarding accidents, where the head strikes a static object [97–99]. Despite the relative plasticity of the neonatal and infantile skull, epidural hematomas also affect children in this age group with equal frequency to that of older children. Skull fractures overlying the site of the epidural hematoma are common and result from the impact injury. Bleeding occurs in the space between the skull and the dura and arises from a ruptured meningeal artery, a torn venous sinus, or from the bone itself. One third of children exhibit the "classic" pattern of immediate unconsciousness followed by recovery (*a lucid interval*) and then secondary deterioration.

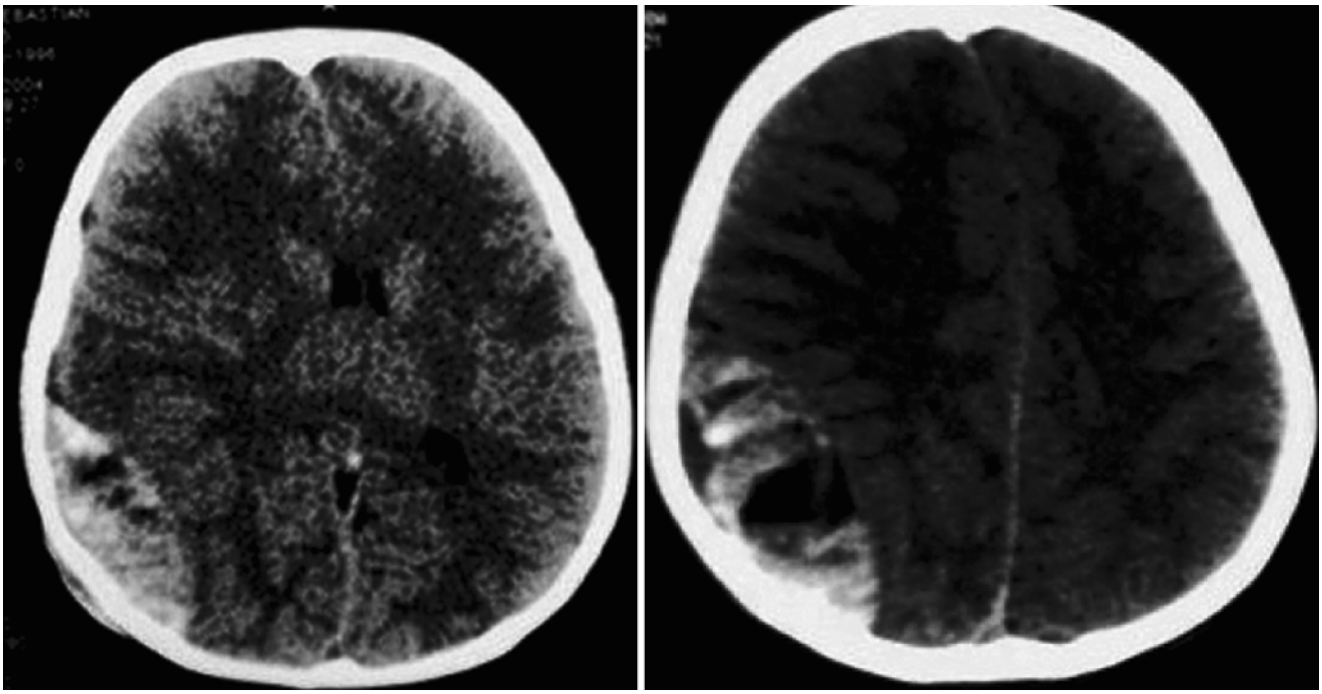

Fig. 14.5 Axial CT scans of an 8-year-old boy who rode his skateboard into a wall 6 h prior to this CT scan. He presented to the ER unarousable with bradycardia and bradypnea. The CT shows an acute epidural hematoma with areas of low density in the hematoma and significant midline shift

This pattern is due to traumatic unconsciousness as a result of the deceleration injury and subsequent recovery from that event, followed by secondary hemorrhage from the epidural vessel, artery, or vein, resulting in increased ICP, cerebral herniation, and loss of consciousness related to brain stem compression. Another third of children are never unconscious and the final third are in coma from the time of the injury [100]. Pupillary changes and hemiparesis are initially found contralateral to the side of the hematoma in only 50 % of children. Therefore, in contrast to adults, the affected side of the hematoma is not easily deduced by clinical examination. If a CT scan cannot be obtained because of the rapidity of the deterioration in the level of consciousness, the best indicator of the location of the clot is the presence of a skull fracture. CT scan is especially sensitive for the presence of epidural hematomas, but if obtained too early the sensitivity decreases as the hematoma has not yet formed [101]. This is most likely in cases of venous epidural hematomas. Any clinical deterioration, including increasing headaches and/or vomiting, requires a second CT scan. Since the outcome is closely related to the level of consciousness at the time of surgical evacuation, early diagnosis is crucial. Low density attenuations found on the CT scan suggest continuing hemorrhage and if seen is an additional indication for early evacuation of the clot (Fig. 14.5). Currently about one-third of epidural hematomas are treated without surgery. Nonsurgical management is more common in awake children and in epidural hematomas that are frontal in location, less than 1.5 cm in size, and unassociated with significant midline shift [102–105]. Many temporal lesions and posterior fossa lesions require surgery because of the risk of rapid deterioration; conservative management (i.e., non-operative) for these lesions has also been described [106–108]. Surgery requires a craniotomy flap and complete evacuation of the lesion with coagulation of any bleeding points. The skull fracture can often be used as one limb of the bone flap and repaired at the time of surgery. Outcome is related to the level of consciousness and the presence of other intracranial lesions. Mortality rates are low from 0 to 5 % and clinical recovery is usually good [98, 99, 102–104, 109], especially in children. ICP monitoring is not necessary in the majority of children after clot evacuation, but if the dura is tight or if there is CT evidence of other intracranial injury, ICP monitoring is generally recommended.

Subdural Hematomas

In the pediatric age group, the majority of subdural hematomas occur in infants and children under 2 years of age who are the victims of child abuse (see chapter on inflicted head trauma). Most subdural hematomas are the result of acceleration/deceleration injuries at high speed and therefore occur after motor vehicle accidents. Both passenger and pedestrian injuries can be associated with subdural hemorrhage. In contrast to epidural hematomas, the bleeding associated with subdural hematomas occurs from tearing of the bridging veins from the cortex to the venous sinuses or from direct

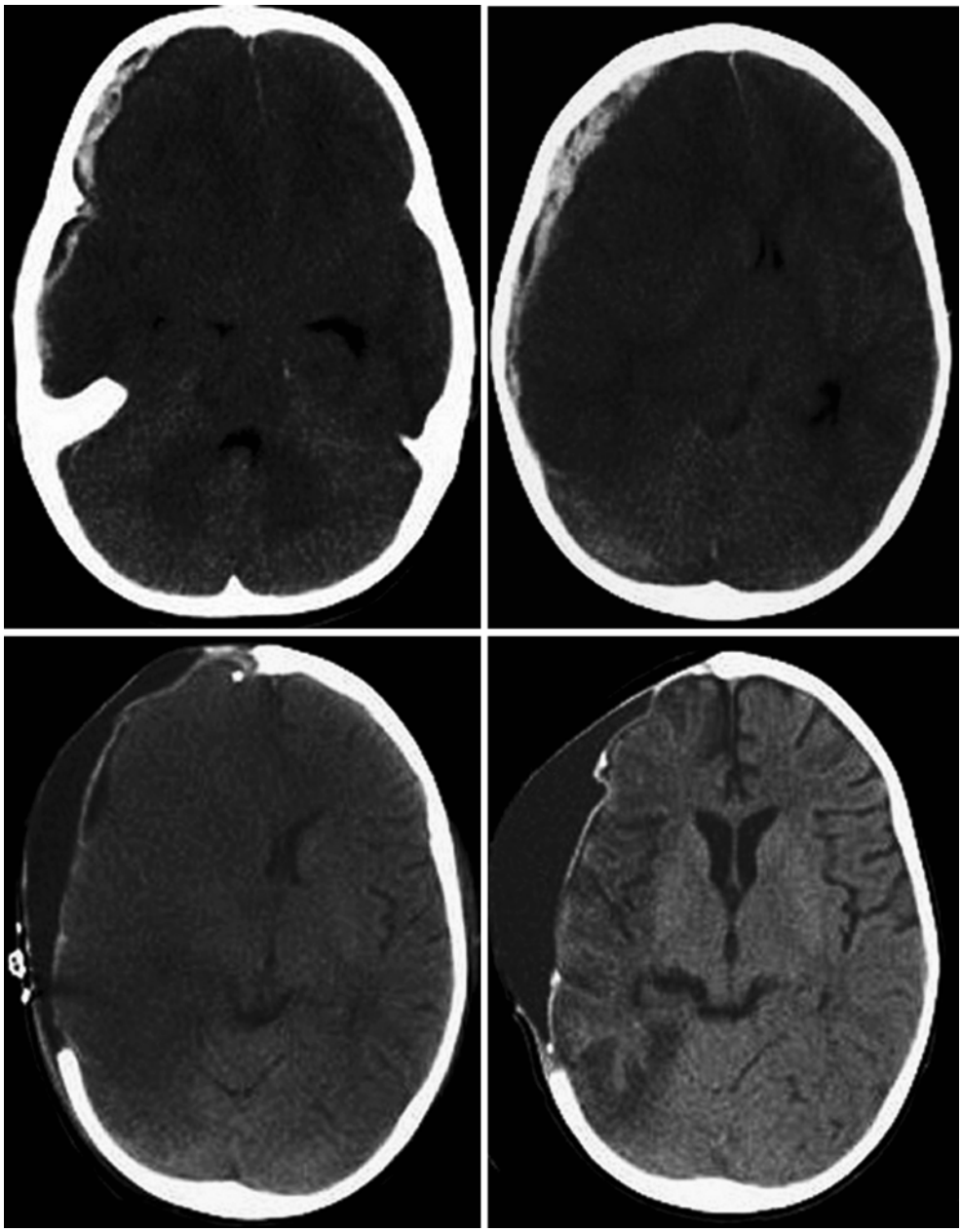

Fig. 14.6 Axial CT scans of a 6 year-old girl who was an unrestrained passenger in a MVA. The *top right* and *left* views demonstrate a small subdural hematoma on the *right*, low-density brain with loss of the *gray/white* interface, and midline shift with trans-tentorial herniation. Because of the inability to control the ICP a decompressive craniectomy was performed after failure of medical management. The *bottom left* view obtained following decompression demonstrates an increase in the low-density area, resolution of the midline shift, and herniation of the hemisphere outside the bony margin. The *bottom right* view obtained after recovery demonstrates evidence of residual damage to the right hemisphere

cortical laceration. The location of the bleeding is usually between the dura and the arachnoid (hence *subdural*), though subarachnoid hemorrhage is also common. As a result of the significant forces required to create subdural bleeding, CT in affected children will frequently demonstrate evidence of other brain injury, cerebral contusions, diffuse axonal injury, intraparenchymal hematoma, or focal or generalized brain swelling. In many cases the size of the subdural hematoma is small compared to the degree of brain herniation (Fig. 14.6). The frequency of surgical drainage of subdural hematomas varies considerably between neurosurgical centers. If the hematoma is not large and the main problem is the underlying brain injury and swelling, medical management of intracranial hypertension may be the only therapy that is required. However, if the hematoma is large and felt to be responsible for the majority of any brain shift seen on imaging, surgical evacuation of the hematoma is indicated. Even after surgery these children frequently require ICP monitoring and aggressive management of intracranial hypertension.

Cerebral Contusions and Intracerebral Hematomas

Children with cerebral contusions often recover without significant sequelae, and resection of contused brain is therefore rarely appropriate. The same is also true for the majority of post-traumatic intracerebral hematomas in children. These lesions are usually small and located in the deep white matter or basal ganglia. They are accompanied by diffuse shearing

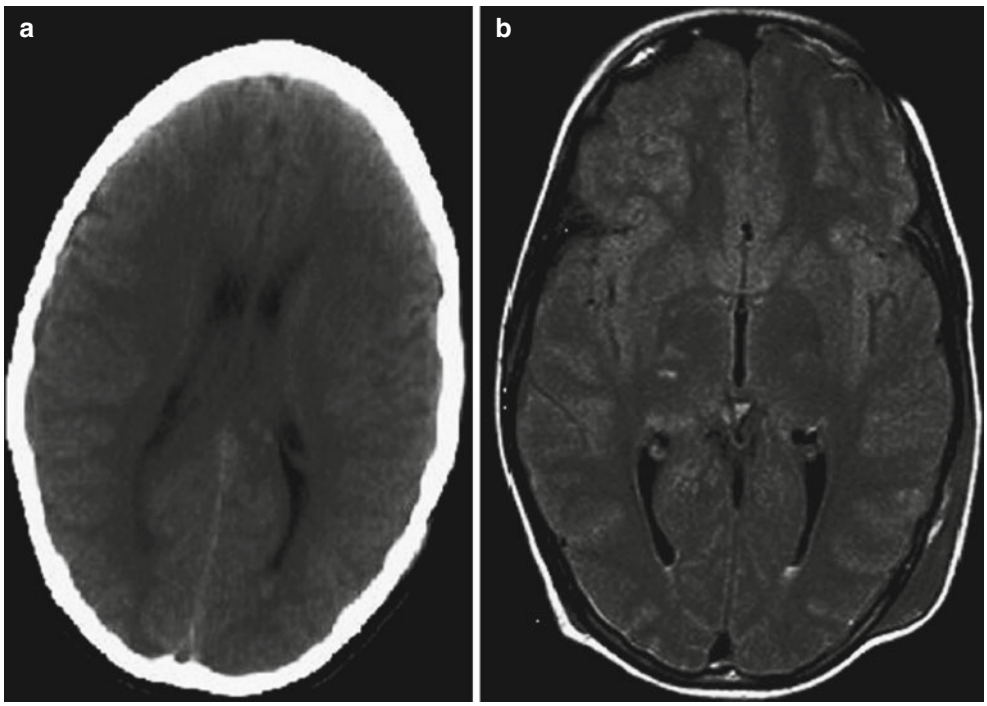

Fig. 14.7 Comparison of CT (**a**) and MRI (**b**) findings on a 6 year-old male who was struck by an automobile. While both imaging studies demonstrate evidence of diffuse axonal injury, the MRI is noticeably superior, showing many more areas of abnormality

injuries in most cases and do not require surgical removal. If one hematoma is progressively enlarging and the ICP cannot be easily controlled, evacuation may be necessary, though as stated rarely necessary.

Serial Imaging

It is now fairly standard practice to repeat a neuro-imaging study at 24 h following injury in all unconscious children because of the frequency with which new lesions or most commonly, progression of lesions are seen [110, 111]. The value of this approach has recently been questioned, as studies have shown that findings on repeat head CT rarely resulted in a change in management [112–115]. In general, serial imaging may not be necessary for patients with an improving neurologic examination. Repeat imaging studies are recommended for any patient with a deteriorating neurologic examination or GCS ≤8 [26, 116]. If an MRI scanner is available, and the patient is medically stable, an MRI is preferable to CT for the follow-up study (Fig. 14.7).

Additional Management Considerations

The child with a TBI poses several critical care management issues, exclusive of ICP and surgical management discussed above. Secondary brain insults may occur at any point after the initial injury and are attributed to both intracranial and systemic factors. Intracranial factors include cerebral edema, mass lesions, intracranial hypertension, vasospasm (with subsequent ischemia-reperfusion injury), and seizures. Systemic factors include hypotension, hypoxia, hyperthermia, hyperglycemia, bleeding due to either coagulopathy or thrombocytopenia [117, 118]. Again, as the extent of primary brain injury is determined at the time of injury and cannot be modified, minimizing the degree of secondary brain injury will ultimately determine outcome.

Electrolyte imbalances are common, especially hyponatremia. As hyponatremia increases the risk of seizures and potentially worsens cerebral edema (both of which can result in worsening ICP and secondary brain ischemia), serum sodium should be monitored closely. Generally, IV fluids should be isotonic (0.9 % saline) [119] without dextrose, unless the child is under 2 years of age (5 % dextrose with 0.9 % saline). In the majority of cases, hyponatremia is due to SIADH (inappropriate secretion of antidiuretic hormone), though the cerebral salt wasting syndrome is not uncommon. A fluctuating situation from SIADH to cerebral salt wasting is not unusual. Hyperglycemia has been shown to worsen outcome following brain injury and should be avoided [40, 120–124]. However, hypoglycemia should be avoided as well [125].

Thrombocytopenia and coagulopathy are especially common following severe TBI and appear to be associated with poor outcome [118, 126–128]. Serial CT scanning suggests that thrombocytopenia and coagulopathy are significant risk factors for developing either new or progressive intracranial hemorrhage following TBI [129–133]. The brain contains a high concentration of tissue thromboplastin [134–136], and in fact, the laboratory assay for plasma thromboplastin time (PTT) at one time was referenced using rabbit brain

thromboplastin [127, 137]. Therefore, TBI results in release of tissue thromboplastin from the injured brain, leading to activation of the extrinsic coagulation pathway. In addition, diffuse endothelial cell damage leads to platelet activation and activation of the intrinsic coagulation pathway, leading to intravascular thrombosis, consumption of platelets and clotting factors, and eventually, disseminated intravascular coagulation (DIC). Intravascular thrombosis certainly contributes to secondary ischemic brain injury as well. Platelet counts, prothrombin time (PT), and plasma thromboplastin time (PTT) should therefore be monitored closely, and if abnormal should be corrected with aggressive replacement of fresh frozen plasma (FFP), cryoprecipitate, or platelets. Of interest, a retrospective review showed that hemorrhagic complications were infrequent in critically ill patients with INR ≤1.6 following ICP monitor placement [138]. While treatment with recombinant activated factor VII has been studied, it generally is not necessary for medical management of TBI and is usually reserved for invasive surgical procedures in the face of a severe bleeding diathesis [139–144].

Neurogenic pulmonary edema (NPE) was initially described in 1908 by Shanahan [145] and colleagues and is defined as noncardiogenic pulmonary edema that occurs in patients with acute CNS disease or injury. NPE has been described in multiple reports and series in both children and adults after seizures, closed head injury, intracranial hemorrhage, penetrating head trauma, and brain tumors [146]. The pathophysiology of NPE is currently poorly understood, but it is thought to be multifactorial in origin. Several theories have been proposed, but it is likely that NPE results from a combination of (i) a centrally mediated catecholamine release (due to acute increases in ICP) leading to increased peripheral vascular resistance and redistribution of blood to the pulmonary circulation and (ii) a centrally mediated increase in capillary permeability [146]. Clinically, the onset of NPE is relatively acute and can rapidly lead to respiratory compromise. Treatment is largely supportive. Of note, several studies have demonstrated the safety of mechanical ventilation with positive end-expiratory pressure (PEEP) in patients with TBI [147–154].

Spinal Cord Injury

Epidemiology

Spinal column injuries are much less frequent compared to head injuries, and are relatively uncommon in children compared to adults [3–5, 155–158]. It is estimated that only 5 % of all spinal cord injuries occur in the pediatric age group with approximately 1,000 new spinal cord injuries reported annually in children age 0–16 years [159]. Most likely, many additional cases go unreported, including immediate fatalities, or those associated with non-accidental trauma or birth-related injuries. Although spinal cord injuries are less frequent in children, the mortality rate is significantly higher as a result of the associated injuries [160]. In addition, detection of spinal injuries in children is more challenging because children are less likely to report symptoms and many injuries are radiographically occult. There is no sex-related difference in the incidence of spinal cord injury in younger children, but in the 10–16 years age group, boys are more likely than girls to sustain a spinal injury [161], probably due to the higher incidence of sports-related injuries.

The mechanism of injury is related to age and behavioral differences. In children less than 10 years old, spinal injuries are usually due to a fall or motor vehicle collision. Abuse accounts for a significant portion of injuries in children less than 2 years of age. In children older than 10 years, motor vehicle accidents and sports-related injuries are the predominant causes of spinal cord injury [162]. While 30–40 % of children with spinal injuries have multiple trauma, only 1–2 % of multiple trauma patients have spinal injuries [3, 5, 155–158, 163] with 19–50 % of these injuries involving the spinal cord [164–166].

Anatomic Considerations

Young children exhibit a different pattern of spinal injury than older children and adults because of anatomic and bio-mechanical differences. For example, infants and to some degree young children have a large head-to-body ratio and poorly developed cervical musculature. In children under 8 years of age, the common levels of injury are the occiput – C1 and C1- C2, while after 8 years of age the lower cervical region -C5, C6 and C7 is most commonly affected (Fig. 14.8). In contrast, in adults cervical injuries constitute only 30–40 % of all vertebral injuries [3, 5, 155–158, 163–169]. Other anatomic factors in children include the increased laxity of spinal ligaments, vertebrae which are not completely ossified, and facets which articulate at a shallower angle. The net result is less skeletal resistance to flexion and rotational forces with more force shifted to the ligaments. This explains why children under 8 years are less prone to spine fractures and more likely to sustain ligamentous injuries. By 8–10 years of age the child's spine adopts a more adult alignment at which time the child's injury profile resembles that of the adult. However, recent studies suggest that injuries to the thoracic spine are the most frequent in children of all ages [169] and that lower cervical injury is more frequently seen in the younger child than previously assumed [170]. The highest risk for spinal injury is in association with severe head injury [171] (Fig. 14.9). Most awake children with spine injuries have local pain and may have a neurological deficit. Spine injury in this setting is rarely truly occult.

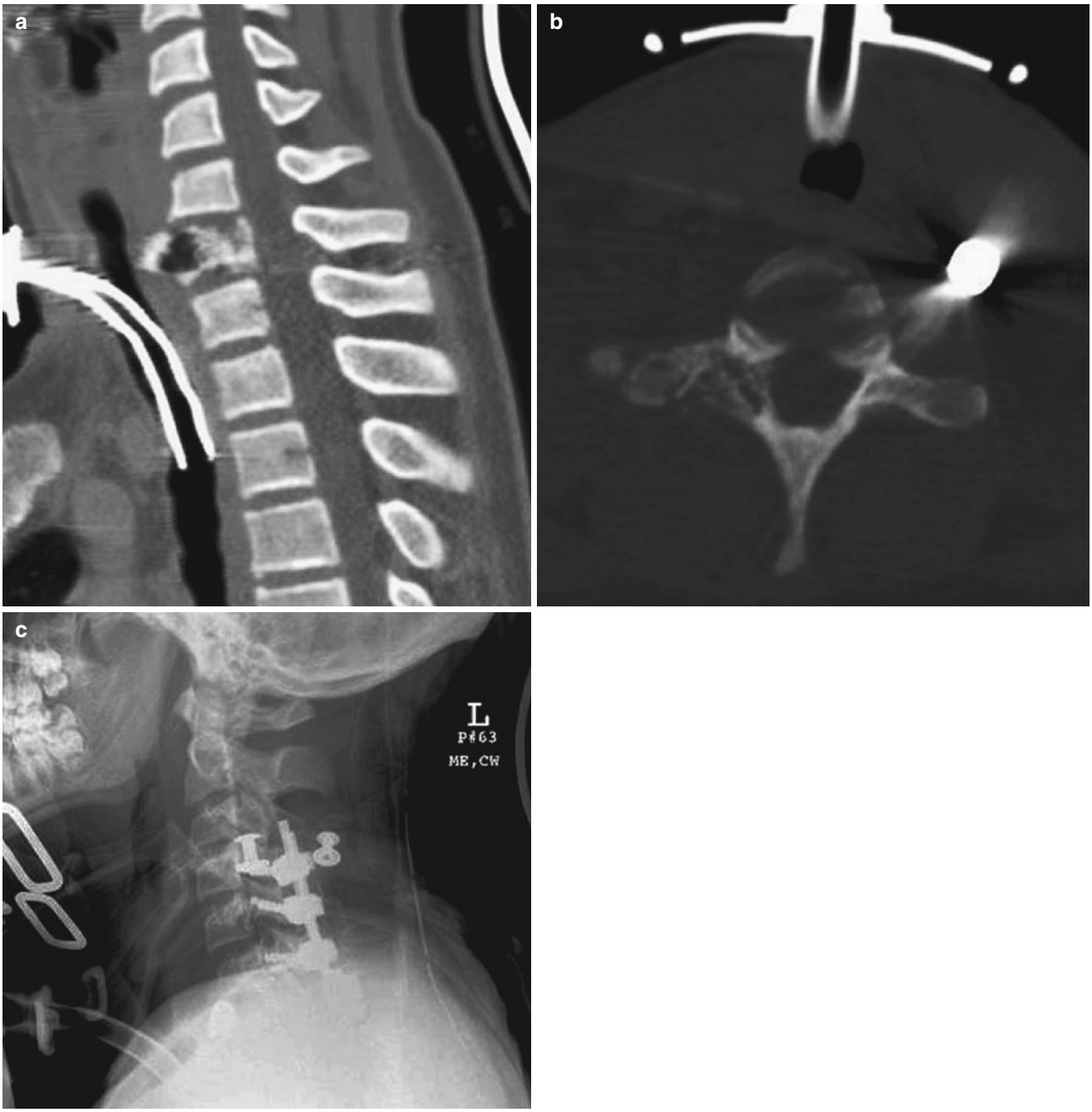

Fig. 14.8 CT scan images (**a**, **b**) of C5 compression, flexion, rotation injury with disruption of the pedicle and transverse process of C5. This is an unstable fracture. (**c**) Post-surgical stabilization lateral spine X-ray

Clearing the Cervical Spine

Clearing the pediatric cervical spine of injury remains a challenge to even the most skilled clinician. Assessing bony tenderness and neurologic deficits in a young child after trauma is difficult. However, if the child does not have midline cervical tenderness, evidence of intoxication, neurologic injury, unexplained hypotension, and distracting injury and has a normal level of consciousness, he/she can be cleared without any radiologic testing. However, this is unreliable in children under 3 years of age – these patients can be cleared clinically if they have GCS >13, absence of no neurologic deficits, midline cervical spine tenderness, painful distracting injury, unexplained hypotension, and the mechanism of injury is not a fall from a height >10 ft, motor vehicle collision, or suspected child abuse. Cervical spine radiographs or high-resolution CT is recommended in the cases not fulfilling these criteria [172, 173]. Anterior-posterior (AP),

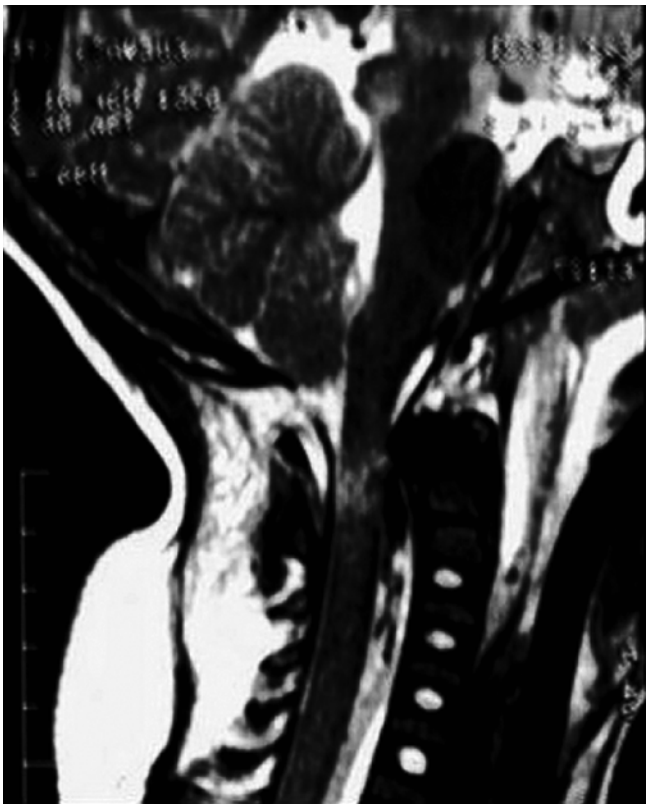

Fig. 14.9 Image is a sagittal T2 MRI scan of a 14 years old boy with a distraction injury at the occiput to C1 (widened occiput to C1 distance), showing intra spinal cord injury and small anterior subdural hematoma. This also shows ligamentous disruption between occiput and C1. He unfortunately had complete tetraplegia without spontaneous ventilation, and initially he was in coma with diffuse head injury. The boy's family wished to continue life support despite a very poor prognosis. This represents an example of a very unstable injury ultimately requiring occiput, C1 and C2 fusion

lateral, and open-mouth cervical spine radiographs are recommended for patients over the age of 9 years who cannot be cleared clinically. High resolution CT, flexion/extension radiographs or fluoroscopy, or MRI are adjuncts to these standard radiographic views [172, 173].

Spinal Cord Injury Without Radiographic Abnormalities (SCIWORA)

SCIWORA is an entity almost unique to children. It was first described in 1982 by Pang and Wilberger as traumatic injury to the spinal cord in children with no fracture or dislocation evident on radiographic tests [174]. SCIWORA occurs most frequently in children under 5 years of age with a frequency of 6–60 % of spinal cord injuries in children [3, 5, 155–158, 163–169, 175–180]. With today's routine use of MRI, most cases previously described as SCIWORA actually do have evidence of injury to the spinal cord itself or ligamentous structures. In fact, with MRI imaging only 12–15 % of these children do not exhibit ligamentous injury and/or spinal cord injury. Several mechanisms have been proposed to explain the pathophysiology of SCIWORA. One possible mechanism is transient vertebral subluxation followed by spontaneous return to normal alignment undetected on plain films. In the process, the spinal cord is pinched between the vertebral body and the adjacent lamina causing injury. A second possible mechanism is that the spinal column is stretched and deformed elastically exceeding the tolerance of the more fragile spinal cord. This stretching can lead to vascular injury of the spinal cord [181]. The probability of recovery of neurologic function is low given that the force needed to disrupt the spinal axis is great typically producing severe injury to the spinal cord [182].

Management

The basic principles of acute management of the spinal cord-injured child are basically the same as with any trauma patient. Interventions include prompt restoration of airway, breathing and circulation. There is no evidence to support an advantage of tracheal intubation over bag-valve-mask ventilation in the pre-hospital setting in the spinal cord injured child. However, there is data reporting a lower rate of successful tracheal intubation in infants and children compared to adults [183] and evidence of further dislocation of the cervical spine during tracheal intubation [184]. Therefore, mask ventilation is an acceptable alternative to immediate tracheal intubation if a skilled clinician is not readily available to perform the procedure. The circulation should be supported with intravenous fluids as in all trauma patients. Patients with spinal cord injury may additionally present with neurogenic shock manifested by loss of sympathetic tone resulting in bradycardia and hypotension. In these instances, fluid resuscitation alone is inadequate to restore circulation, and so vasopressors such as dopamine or norepinephrine should be used early in the resuscitation.

Complete, neutral immobilization of the spinal axis is vitally important in any child with suspected spinal injury to prevent movement and possible exacerbation of the spinal cord injury. An appropriately sized cervical collar should be placed and the child should be on a backboard. Care should be taken to avoid using collars that are too large as they can distract the neck excessively and worsen injury. Backboards for young children should have a recess for their disproportionately large occiput to avoid inadvertently placing the neck in flexion. If such a board is not available, a small shoulder roll should be placed. In children under 5–6 years of age the standard backboard tends to result in a flexed neck and is often not satisfactory. In the unconscious child manual

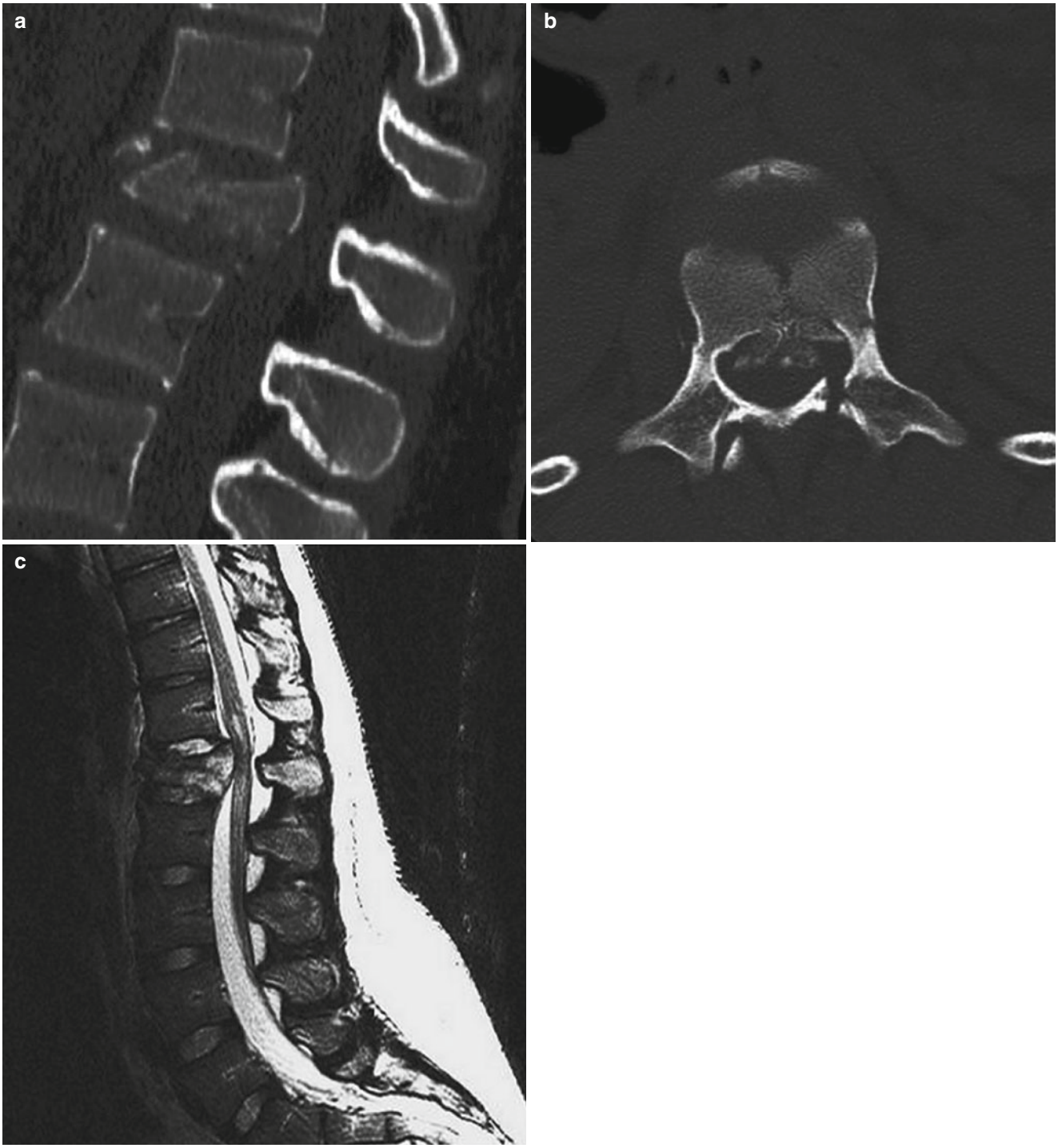

Fig. 14.10 CT scan images (**a**, **b**) of a 10 year-old boy who was a passenger in the rear seat demonstrating evidence of L1 burst fracture with displacement of bone into the spinal canal. The T2 MRI sagittal image (**c**) shows a vertebral fracture, bony displacement into the canal, and signal change in the conus. The neurological exam showed a complete paraplegia from T12 down. This was a lap belt injury and the fracture required surgical fusion of T11- L3

support or sand bags are preferable to a poorly fitting collar or backboard. In addition many injuries in children have a traction component and thus further traction is not advisable (Fig. 14.10). This occurs when poorly fitting collars are used. The neutral position without flexion or extension and without traction is ideal for transport, but this is hard to achieve in the child.

Spinal immobilization is maintained until either the child awakes and an exam can be conducted or the spine is cleared after MRI. Hypotension in the absence of definable blood

loss should trigger the suspicion of a spinal cord injury and may require both volume and vasoactive medication. Acute bladder distension can occur after fluid resuscitation if the spinal cord is injured leading to severe hypertension. A bladder catheter should be placed as soon as the absence of urethral injury is established. If the child is on a backboard this should be removed as soon as possible as skin breakdown can occur within a few hours after spinal cord injury.

If there is clinical or radiological evidence of spinal cord injury an early MRI should be performed to establish the state of the spinal cord and to identify any evidence of spinal cord compression or injury. With the presence of significant cord compression acute surgical decompression may be necessary with bony stabilization. Unstable spinal fractures, even in the absence of spinal cord compression may require early surgical stabilization. In the severely head injured child with increased ICP, time to surgical intervention is an individual decision. Earlier surgery may shorten the PICU and acute hospital stay without evidence of improved neurological outcome.

If a spinal cord injury is present, the child should be admitted to the PICU utilizing a bed that is appropriate for a spinal cord injury allowing for easy and frequent changes of position. An acute illeus may be present and require the placement of a nasogastric tube for decompression. Skull traction is rarely indicated in children <8 years of age. Maintenance of normal cardiovascular and respiratory parameters is the same as for head injury. Deep venous thrombosis is a serious risk especially in younger children. Low dose heparin is begun as soon as the cranial or other injuries make this possible. High-dose corticosteroids are the standard of care in many hospitals for spinal cord injured adults and children despite on-going controversy regarding their effectiveness. The current recommendation is to give an initial iv bolus of 30 mg/kg of methylprednisolone followed by an iv infusion of 5.4 mg/kg/h for 24 h if started within 3 h of the injury and for 48 h if started 3–8 h after the injury. These recommendations are based on the results of the National Acute Spinal Cord Injury Study I, II, and III (NASCIS I, II, and III) and follow-up studies [185–191]. A brief discussion of these studies is pertinent to the present discussion.

NASCIS I was a multicenter, double-blind randomized trial comparing high-dose methylprednisolone (1,000 mg bolus followed by 1,000 mg once daily for 10 days) versus standard-dose methylprednisolone (100 mg bolus followed by 100 mg once daily for 10 days) in 330 adults with acute spinal cord injury. This study failed to demonstrate any significant differences in neurological improvement at 6 weeks and 6 months after injury between groups, and in fact, there was a trend towards an increased incidence of wound infection and mortality in the high-dose methylprednisolone group [185]. These differences persisted at 1 year follow-up [186]. Unfortunately, the lack of a placebo group precluded any meaningful findings from this study on the efficacy of corticosteroids in acute spinal cord injury. However, near the conclusion of the NASCIS I study, preclinical data from animal studies suggested that the dose of methylprednisolone used in that study was below the therapeutic threshold of approximately 30 mg/kg body wt [192].

NASCIS II was a multicenter, double-blind, randomized trial comparing methylprednisolone 30 mg/kg followed by a continuous infusion of 5.4 mg/kg/h for 23 h, naloxone (5.4 mg/kg bolus followed by 4 mg/kg/h infusion for 23 h), and placebo involving a total of 487 adults treated within 12 h of presentation with acute spinal cord injury [187]. Again, there were no significant differences in neurological recovery between the three groups at 6 weeks, 6 months, and 1 year following injury [187, 188]. However, a post-hoc analysis (unplanned) suggested that patients who were treated in the methylprednisolone arm within 8 h of injury demonstrated significant improvements in neurological recovery at 6 weeks, 6 months, and 1 year following injury [187, 188]. While the exact numbers were not reported, less than 50 % of the patients that were enrolled in the study received treatment (methylprednisolone, placebo, or naloxone) within 8 h of injury. Notably, patients treated with methylprednisolone after 8 h following injury had worse outcome, suggesting that corticosteroid treatment could be detrimental in some patients with acute spinal cord injury.

NASCIS III was a multicenter, double blind, randomized trial comparing methylprednisolone (30 mg/kg bolus followed by a continuous infusion at 5.4 mg/kg/h) infused for a total of either 24 or 48 h to tirilazad mesylate in 499 adults with acute spinal cord injury [189]. Again, no significant differences in neurological recovery were demonstrated between the 24 and 48 h infusions of methlyprednisolone, although though a post-hoc analysis (unplanned) suggested that patients who received treatment within 3–8 h of injury had significantly improved neurological recovery at 6 weeks, 6 months, and 1-year after injury [189, 190].

Numerous methodological concerns exist with the design, statistical analysis, randomization, and clinical endpoints used in all three NASCIS studies [193–199]. In addition, a prospective, randomized clinical trial conducted in 106 adults with spinal cord injury in France failed to replicate the results of NASCIS studies [200]. Furthermore, there are no data in children to support or refute the efficacy of corticosteroids in spinal cord injury. Outcomes in patients treated with this high dose steroid protocol have been disappointing [201], and a publication by the Congress of Neurologic Surgeons and American Association of Neurologic Surgeons after reviewing the National Acute Spinal Cord Injury Study data, stated that the evidence suggesting harmful side effects of methylprednisolone is more compelling than any suggestion of clinical benefit [202]. However, many physicians continue to prescribe corticosteroids in patients with

acute spinal cord injury (despite these data and the position statement referenced above) due to fears of possible litigation [203, 204], and so it is likely that this controversy will be debated for years.

Conclusion

While overall mortality rates have decreased significantly, TBI remains a significant public health problem. In addition, while cervical spine and spinal cord injuries are less common in children compared to adults, these injuries are an important cause of long-term morbidity and pose a significant burden on the health care system. The management of these injuries has evolved over time. Critically injured children with TBI require the close coordination of management between the PICU team, the trauma surgeon, and the neurosurgeon.

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Craniofacial Trauma

15

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Abstract

Management of the pediatric facial trauma patient presents a unique challenge to the clinician given the differences in anatomy, physiology and psychological development compared to the adult patient. These differences account for the overall low incidence of these injuries in the United States. Although many of these craniofacial injuries are treated in a conservative fashion, a high index of suspicion, and a thorough clinical exam should guide treatment even in the setting of normal radiographic studies. Often a multidisciplinary surgical team is needed to treat the various components of these complex injuries, especially considering the long-term effects that treatment may have on growth and development. This chapter discusses the treatment of frontal, orbital, nasal, mid-face and mandibular fractures, in addition to the management of soft tissue injuries as they pertain to the pediatric critical care specialist.

Keywords

Pediatric facial trauma • Pediatric facial fractures • Treatment and management of facial trauma

Introduction

The management of the pediatric facial trauma patient presents a unique challenge to the clinician given the differences in anatomy, physiology and psychological development compared to the adult patient. While the principles of management are in essence the same, the techniques utilized to evaluate and treat the injury must be modified based upon the injured child's age. Thus, the clinician must consider the potential impact on long-term craniofacial growth and development as treatment plans are formulated. The goal of this chapter is to present a concise review of pediatric facial injuries, including the evaluation and management as it pertains to the pediatric critical care specialist.

Epidemiology

In comparison to the adult population, pediatric facial fractures in the United States are uncommon, comprising only 15 % of all facial fractures and decreasing in incidence proportionately with age [1, 2]. These statistics are directly attributable to the inherent differences in anatomy, physiology and social factors that exist between adults and especially pre-adolescent children. Statistics from the 2010 National Trauma Data Bank pediatric report demonstrate an increased incidence of craniofacial trauma in males, most commonly due to motor vehicle accidents and falls. Other etiologies include violence and sports-related injuries,

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especially in adolescents, as well as child abuse. Similar to general pediatric trauma, the frequency of craniofacial injuries increases during the winter and summer months when children are not attending school [3].

Anatomic and Physiologic Considerations in Pediatric Craniofacial Injuries

The concept that is repeatedly emphasized in this chapter is the anatomic and physiologic differences of the craniofacial skeleton in the pediatric population compared to adults. The key characteristics that separate the two populations are surface area, structure and skeletal elasticity. In regards to surface area, children have small faces in comparison to the size of their heads. The ratio of cranium size to face decreases throughout childhood and stabilizes during adolescence to a ratio of 2.5:1 [4]. Structurally, facial projection increases throughout childhood although the composition of the craniofacial skeleton also changes over the course of development [5]. Dense facial fat pads, unerupted teeth in both the mandible and maxilla, in addition to unpneumatized sinuses pad and protect the face from fractures. Finally, there is increased elasticity of the skeleton compared to adults, leading to a higher incidence of greenstick and non-displaced fractures [6]. Although these properties contribute to the decreased incidence of facial fractures in children, the clinician must not discount the possibility of injuries to the underlying brain in both the presence or absence of a fracture. It follows then that the severity of the fracture positively correlates with an increased incidence of concomitant injuries [6, 7]. In addition, fractures located in facial growth centers (i.e. nasal septum and mandibular condyle) can have a significant impact on future facial growth (Fig. 15.1).

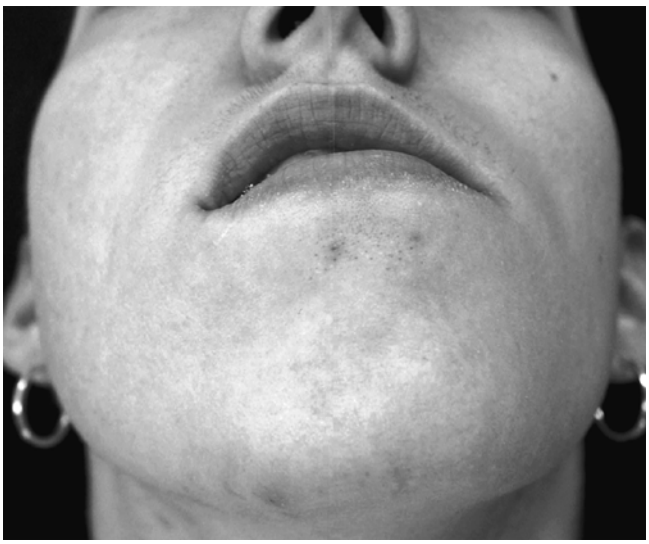

Fig. 15.1 Mandibular asymmetry secondary to a history of a left condylar fracture

Clinical Examination

The management principles of Advanced Trauma Life Support are broadly applicable to both children and adults. When considering the ABCD's of trauma, the airway is of particular importance in the setting of facial trauma as it can be compromised by fractures, swelling and bleeding. Children specifically possess a high surface area-to-volume ratio, which in cases of severe intravascular volume depletion, can lead to rapid decompensation. However, children and adolescents possess a greater physiologic reserve than adults and their compensatory mechanisms may mask early signs and symptoms of volume depletion. Thus, aggressive volume resuscitation is important in initial management. Once the patient has been stabilized, a comprehensive physical examination can be performed.

A detailed examination of the head and neck of an injured child can pose multiple challenges secondary to patient anxiety and often an inability of the patient to verbalize an exact complaint. If the patient cannot provide a history, an account from the caregiver or a witness describing the mechanism of injury can help focus the physical exam. In some cases, sedation and restraints may be required to obtain an adequate exam; however, the airway must be stable or secured prior to examination. The examination should be performed in a systematic fashion beginning cephalically and proceeding caudally. Starting with superficial inspection, the clinician should catalogue any superficial lacerations or gross deformation. This is followed by gentle palpation of the face, noting any step-offs, asymmetries and crepitus, although significant edema can mask underlying deformities.

Special attention should be given to the ophthalmic, nasal, dental and cranial nerve examinations. Any gross disturbances or the inability to assess the visual acuity, pupillary response to light or extraocular muscle function warrants consultation with ophthalmology. In addition to evaluating for fractures, a thorough examination of the nose includes an evaluation of the nasal airway to rule out septal hematoma and cerebrospinal fluid leakage. These findings will be addressed in subsequent sections of this chapter.

Malocclusion of the teeth is a sensitive indicator for both maxillary, mandibular and dentoalveolar fractures. Even in an uncooperative child, if the teeth cannot be assessed for mobility or the gingiva evaluated for lacerations, many children will demonstrate their occlusion. Finally, an abnormal cranial nerve examination may indicate an underlying fracture in the setting of an otherwise equivocal physical exam.

Imaging Studies

When considering the use of diagnostic imaging, it is important to consider the nature of the injury. If the mechanism of trauma is significant, or the history is unclear, a CT scan of the head and entire face is indicated. The combined study eliminates the need for an isolated facial CT, reducing additional radiation exposure and the cost of another study [8–10]. Spiral and multi-slice techniques have reduced the dose of radiation significantly when compared to old CT methods [11]. Due to the difficulty with movement of the child during radiologic procedures like CT scanning, sedation or anesthesia may be necessary to ensure adequate imaging. But this must be approached with caution, as it may obscure neurologic injury and assessment.

Multiple CT scan planar views (coronal, axial, sagittal) with 3-D reformatting will confirm the location and extent of skeletal, soft tissue and visceral injuries (brain or eye trauma). Axial images help assess the orbital volume in maxillary and zygomatic fractures while coronal projections are important to assess nasoorbitoethmoid fractures. Coronal images also help identify extraocular muscle entrapment. This is particularly helpful in patients who have been immobilized in a cervical collar. 3-D reformatting gives the most accurate assessment of fracture patterns. In general, plain film X-rays are not indicated due to the difficulty with interpreting them secondary to unerupted tooth buds in children. For isolated mandible fractures, the panoramic tomogram provides an excellent image of the entire mandible. It has the advantage of showing the fracture pattern and also the location of the tooth buds.

Principle of Fracture Management

In general, pediatric facial fractures are managed more conservatively than in adults. This is not to say that the principles of fracture management should be abandoned. Fracture reduction and immobilization are still of paramount importance. A conservative approach is indicated in part because of the increased incidence of mildly displaced and greenstick fractures, which in many cases are non-operative. Additionally, careful consideration must be given if open reduction and internal fixation is undertaken since there is a potential to disrupt growth centers of the facial skeleton. If open reduction is required, the timing of the operation must be considered both by the surgeon and the intensive care team. Otherwise, healthy pediatric patients have a propensity to heal soft tissue and remodel bone faster than adults [12, 13]. While this necessitates earlier operative intervention to prevent malunion, an advantage is that the duration of immobilization can be reduced. If possible, it is our practice to intervene within a week of the injury. If an operative intervention is delayed longer than a week, healing may occur which will make fracture reduction more difficult. The primary indications for emergent intervention are extraocular muscle entrapment, retrobulbar hematoma which may manifest as superior orbital fissure and orbital apex syndrome, and finally hemorrhage.

Frontal Fractures

As previously indicated, the ratio of the skull size to the face decreases as children age, anatomically predisposing younger children to skull fractures and older children to facial fractures due to the increased projection of their face [14]. The management of frontal bone fractures also changes depending upon the age of the child and the development of frontal sinuses, which do not begin to pneumatize until after 5 years of age. Prior to development of the frontal sinuses, non-displaced frontal bone fractures are managed non-operatively. If the fracture is displaced, involves the naso-frontal duct, or if there is persistence of a cerebrospinal fluid (CSF) leak, exploration is indicated [4]. In older children with developing frontal sinuses, the management becomes more complicated. Although non-displaced fractures of the anterior table are also managed non-operatively, displaced fractures causing contour irregularities may require operative management (Fig. 15.2). Fractures involving the posterior wall may require a multidisciplinary effort given the potential for persistent CSF leaks, shunt management, dural repair, and need for cranialization or obliteration of the frontal sinus (Fig. 15.3). If a CSF leak is suspected, non-specific signs such as the halo sign or ring test should not be used. Rather, testing for the presence of beta-2 transferrin in the setting of rhinorrhea is both highly sensitive and specific for a leak [15].

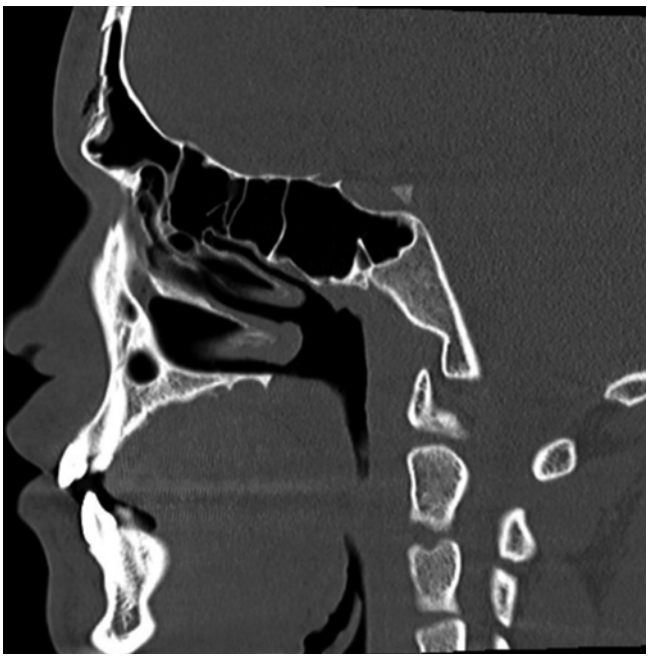

Fig. 15.2 Displaced fracture of the anterior table of the frontal bone

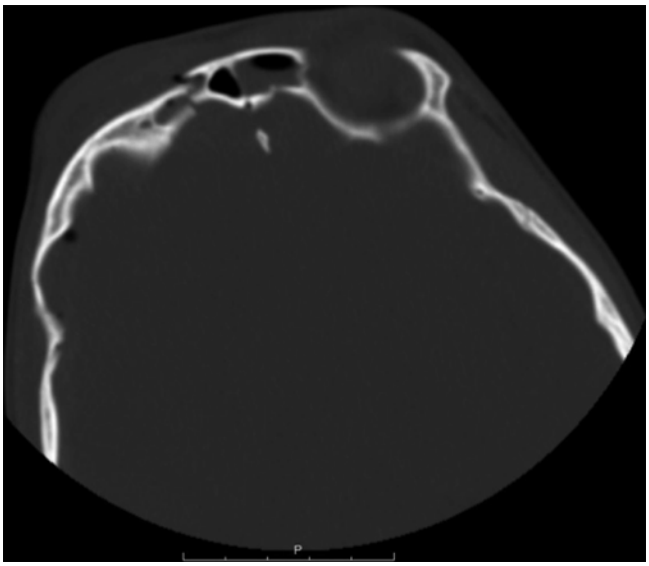

Fig. 15.3 Displaced fracture of the frontal bone involving both the anterior and posterior walls

Orbital Fractures

The indications and timing of operative intervention for orbital fractures is a controversial subject and beyond the scope of this chapter; however there are several indications that require emergent operative intervention that must be clinically identified (Fig. 15.4). Beyond injuries to the globe, orbital fractures that lead to extraocular muscle (EOM) entrapment and/or retrobulbar hematoma must be addressed immediately. As with frontal bone fractures, orbital fractures are best managed with a multidisciplinary approach involving ophthalmology, especially when injuries to the globe or changes in visual acuity are suspected.

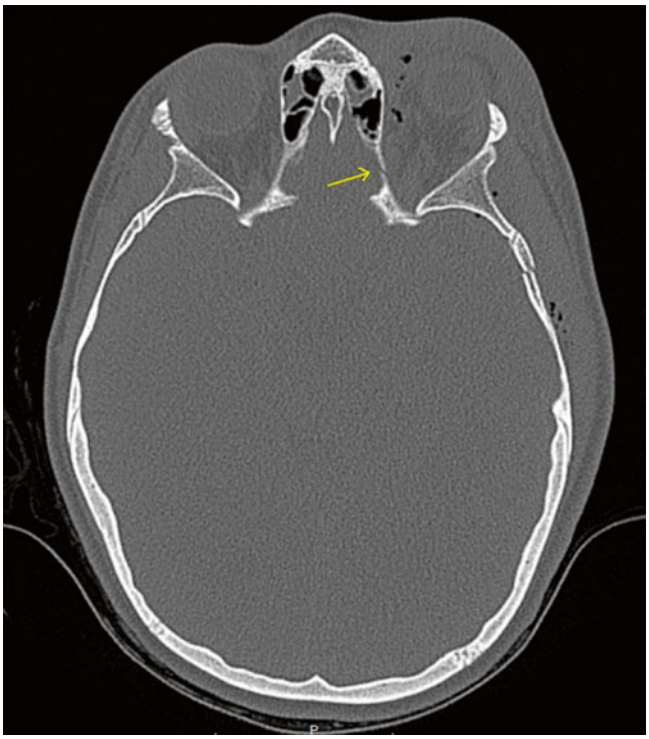

Fig. 15.4 Non-displaced fracture of the medial orbital wall (*yellow arrow*)

EOM entrapment occurs most frequently in conjunction with fractures of the orbital floor. In children, a greenstick-like fracture of the orbital floor can result in EOM entrapment as the fracture hinges shut on the soft tissue elements of the periorbita, acting as a "trapdoor." Entrapment manifests itself as diplopia secondary to restrictions in both vertical and horizontal gaze coupled with nausea and vomiting (Fig. 15.5). Bradycardia may also ensue as a result of the oculocardiac reflex. A forced duction test should be employed if the patient is sedated or cannot cooperate with the exam. Surgical intervention is indicated emergently to prevent necrosis of the inferior rectus and inferior oblique muscles, in addition to relieving the oculocardiac reflex [16].

Significant retrobulbar hemorrhage becomes a surgical emergency as blood accumulates behind the orbital septum, resulting in an orbital compartment syndrome. Orbital blowout fractures generally do not lead to increased compartment pressure since the edema and hemorrhage is decompressed into the adjacent sinuses. Clinically, increased periorbital pressure manifests initially as pain, but later as superior orbital fissure syndrome and orbital

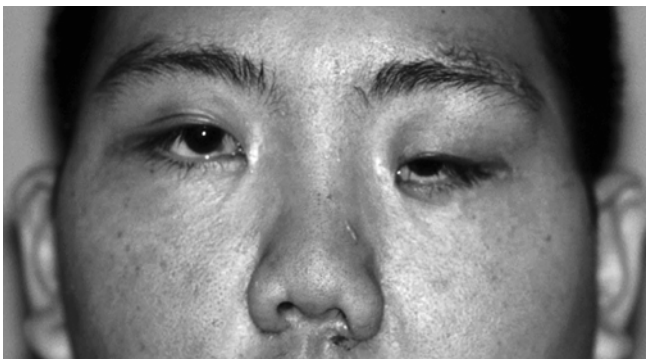

Fig. 15.5 Left inferior oblique muscle entrapment due to an orbital floor fracture

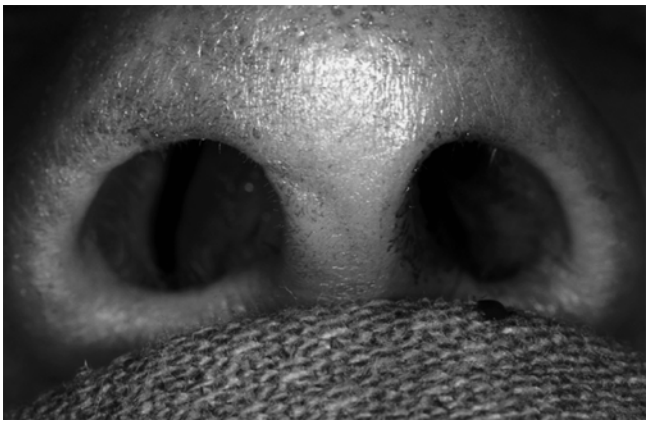

Fig. 15.6 Right-sided deviation of the nasal septum secondary to a nasal fracture

apex syndrome. Superior orbital apex syndrome is characterized by diplopia, paralysis of the extraocular muscles, exophthalmos and ptosis. When vision loss is compounded with superior orbital apex syndrome, the associated signs are referred to as orbital apex syndrome. Upon recognition of these signs, medical treatment should be initiated immediately. Mannitol, acetazolamide, systemic and topical steroids are given concurrently to assist in minimizing edema [17]. Surgical decompression including lateral canthotomy, release of the orbital septum, reduction/removal of orbital fracture fragments, evacuation of the hematoma and hemostasis must be performed within 1 h to prevent permanent vision loss [18].

Nasal Fractures

The composition of the nasal pyramid in a child is virtually identical to that of an adult, however, it is the structural make-up that differentiates the two. During pre-adolescence, nasal fractures are uncommon given the relative small size of the nasal bones, their lack of projection, and the compliant cartilages that compose the nasal tip. For these reasons, blunt trauma to the mid-face generally does not result in a nasal fracture for younger children, given that the adjacent maxillary and zygomatic buttresses absorb the force of trauma. If a nasal fracture is encountered on physical exam, the index of suspicion should be high for potential injuries to the nasal septum, orbital bones and nasoorbitoethmoid fractures, which should prompt a CT scan [19]. Upon reaching adolescence, the fracture pattern of a child with a nasal injury will more closely resemble that of an adult, due to the increased projection, size of the nasal bones, as well as the increased rigidity of the cartilages.

In all cases, evaluation of the septum is a critical aspect of the nasal exam. Examination with a speculum will rule out the presence of a septal hematoma which if left untreated, can lead to necrosis of the septal cartilage and collapse of the nasal dorsum (saddle nose deformity). In addition, failure to address septal deviation caused by a fracture can lead to nasal obstruction (Fig. 15.6). Closed reduction of both the septum and nasal bones is best performed within 1 week of the inciting event. If treatment is delayed beyond 2 weeks, open techniques may be required; however, secondary deformities are best addressed once the patient reaches skeletal maturity to prevent growth disturbances [20].

Zygomaticomaxillary Complex Fractures

Zygomaticomaxillary complex (ZMC) fractures are relatively uncommon in children due to the lack of prominence of the malar eminences, and lack of pneumatization of the paranasal sinuses. They are usually caused by high velocity motor vehicle crashes. A significant force is required to fracture the ZMC, thus when present, the clinician should have a high index of suspicion for neurocranial involvement. Physical findings may include: periorbital ecchymosis, subconjunctival hemorrhage, and anesthesia over the zygomatic arch, lateral nose and upper lip. There may also be depression or lack of projection of the malar eminence (Fig. 15.7). Due to the orbital component associated with these fractures, an ophthalmologic consultation is mandatory.

Minimally displaced fractures with little or no loss of facial projection, and no ophthalmologic involvement should be treated conservatively with observation. Fortunately, comminution of the zygoma is rare in children; however, for significantly displaced fractures, open reduction and fixation is required. This can be achieved through multiple surgical approaches. Wide stripping of the periosteum should be avoided to prevent the adverse consequences of periosteal scarring on future growth. Also caution should be exercised to avoid screw placement through unerupted teeth in the primary or mixed dentition.

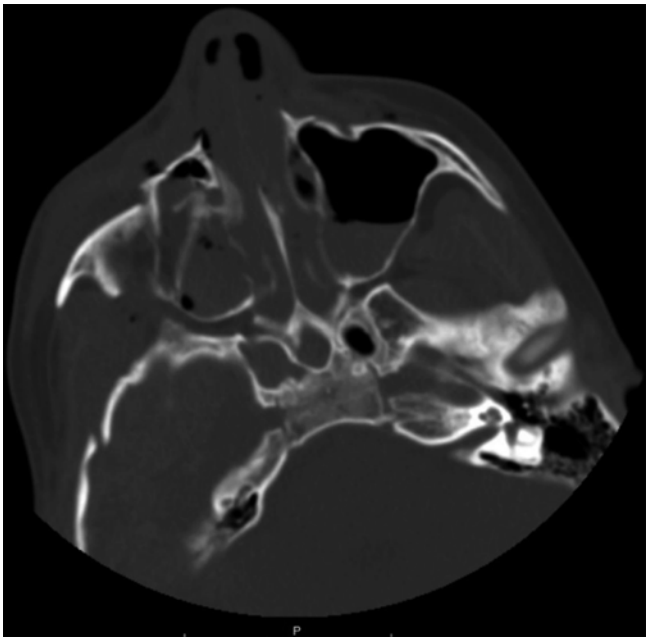

Fig. 15.7 Right zygomaticomaxillary complex fracture

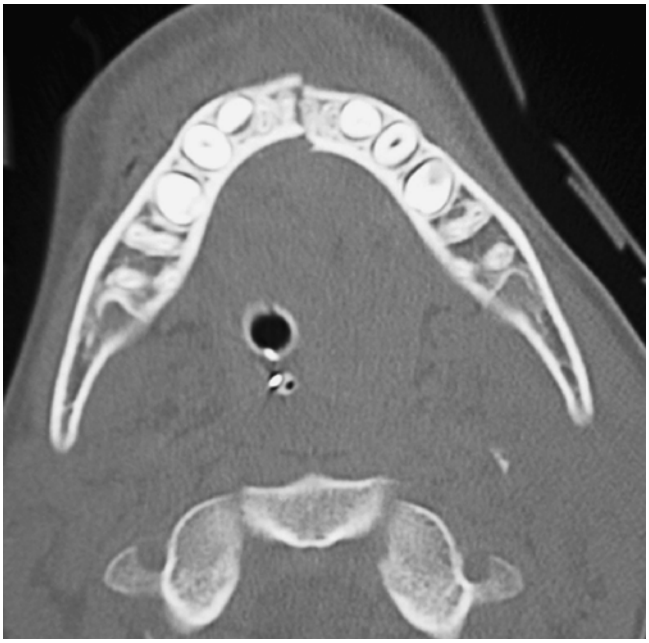

Fig. 15.8 Mandibular symphysis fracture

Maxillary Fractures

Similar to ZMC fractures, fractures that involve the middle third of the face are very uncommon in children. This is due to the presence of unerupted teeth stabilizing the bone, in addition to the lack of pneumatization of the paranasal sinuses. They are usually seen with high impact motor vehicle collisions and therefore other injuries should be suspected. The paranasal sinuses start to rapidly develop after 6 years of age, so that maxillary fractures in children do not follow the same patterns as seen in adults. Thus, classic LeFort fracture patterns are rarely seen in the pediatric population. These fractures usually have an associated dentoalveolar component with tooth fracture or avulsion, and gingival lacerations. Clinical examination to determine mid-face stability is paramount, as CT scans may not detect mid-face fractures. Minimally displaced fractures should be managed with closed reduction when malocclusion is present. This can be achieved through the use of arch bars. Significantly displaced fractures causing an anterior open bite or posterior displacement of the mid-face require open reduction and internal fixation [21]. Care must be taken to avoid injury to the developing dentition with screw placement. In extreme cases, the facial buttresses may be restored with bone grafts to restore facial width and projection.

Mandibular Fractures

Mandible fractures comprise approximately one-third of facial trauma in children, and are the leading cause of hospitalization in pediatric facial trauma. Common causes include falls, sports and bicycle accidents. Males are more affected than females. Mandibular fracture patterns may change given the fact that the child's jaw is filled with teeth at various stages of development at different chronological ages. Additionally, the mandible is the last bone in the face to reach skeletal maturity, and as such is vulnerable to growth related injuries since injuries are more likely in late childhood and adolescence. An analysis of pediatric mandibular fractures reveal that 55 % involve the condyle, 35 % the body, and 10 % are seen in the angle of the mandible [22]. Despite the high incidence of condylar fractures, a significant number of these remain undiagnosed. As the child grows and the bone matures, the incidence of symphyseal and body fractures increase, mimicking adult mandible fracture patterns (Fig. 15.8).

Physical findings include: pain at the site of fracture, malocclusion, jaw deviation upon opening, jaw instability, chin lacerations and intraoral ecchymosis. Chin lacerations and/or blood in the external auditory meatus should alert the clinician to carefully look for condylar fractures as the impact to the chin is transmitted to the condyles [23].

A conservative approach to management is generally undertaken since the growing mandible has a high remodeling capacity that frequently compensates for less than ideal reduction and alignment. In minimally displaced fractures with no malocclusion, observation and of soft diet are indicated. Depending upon the physical examination and CT scan findings, mildly displaced fractures may be amenable to closed reduction and maxillomandibular fixation. Arch bars can be placed sufficiently between the ages of 2 and 5 years as the deciduous teeth have firm roots. Between 6 and 12 years of age, there is rapid root resorption that may require extra support from circummandibular wiring and pyriform aperture suspension. Long periods of immobilization should be avoided as it can lead to TMJ ankylosis.

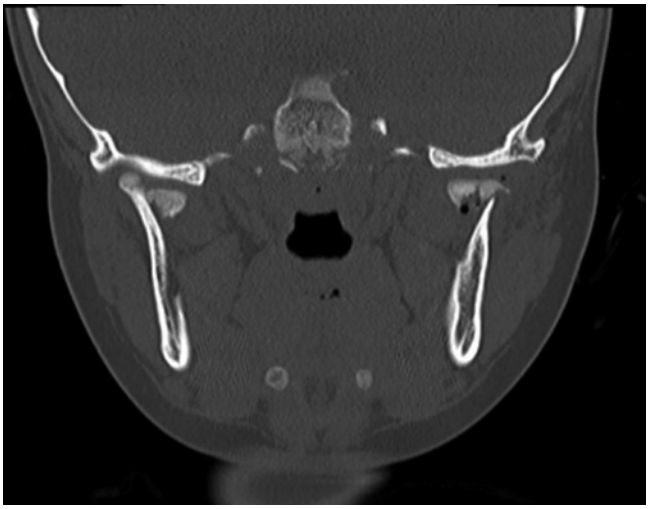

Fig. 15.9 Bilateral fractures of the mandible involving the condyles

Condylar fractures in children require long term follow-up at regular intervals until completion of mandibular growth (Fig. 15.9). The incidence of growth disturbances increases with intracapsular fractures that are often seen in early childhood. Should asymmetry begin to develop in the early post-injury phase, referral to an orthodontist is mandatory. Proffit et al. have reported that up to 10 % of patients with dentofacial deformities had evidence of a previously undiagnosed condyle fracture [24].

Dentoalveolar Fractures

Dentoalveolar fractures are very common injurries that involve the teeth and their housing, the alveolar process. They are underreported since they are usually managed in the emergency department of at outpatient visits in dental offices. The clinical presentation is gingival hemorrhage combined with gross mobility of at least a two-tooth segment. The teeth may be displaced or avulsed from their sockets. The treatment follows similar management of other fractures of the jaws. The displaced segment is reduced with gentle traction to restore occlusion. The segment is then stabilized using arch bars or a wired splint for 6 weeks. The affected teeth are followed long term for the possibility of pulpal necrosis. Avulsed deciduous teeth are not replaced into their sockets unlike permanent teeth that should be replaced within 1 h. Follow up with a pediatric dentist is essential to monitor for ankylosis of primary teeth, which may prevent the normal eruption of permanent teeth.

Soft Tissue Injuries

Facial soft tissue injuries occur quite frequently in children secondary to the disproportionately large surface area of their face, as well as their active, inquisitive nature. The mechanism of these injuries varies from sports, falls, motor vehicle accidents, assault and animal bites. The superficial nature of these injuries however should not overshadow the potential functional, cosmetic and psychological sequelae for the patient and their family.

Prior to treatment, the patient care team should decide whether treatment should be performed in the emergency department, at bedside or in the operating room. The complexity of the wound, the time needed for repair, and the ability to deliver adequate sedation and anesthesia must be weighed. With the aid of sedation, weight-based local and regional blocks can be administered using lidocaine with epinephrine and bupivicaine. Topical anesthetics can be useful in smaller wounds, but the onset of anesthesia can take up to an hour and supplemental local infiltration is often needed.

The central tenets of wound closure are copious irrigation, adequate debridement of devitalized tissue, and tension free closure. Loose debris contaminating the wound should first be removed, followed by irrigation with normal saline. Debridement of the wound edges should be performed in a judicious fashion given the rich blood supply in the face. Closure of the wound is then performed in layers, approximating the lacerated structures preferably with interrupted resorbable monofilament sutures. These deeper sutures aid in preventing scar spread, relieving tension on the superficial layer of sutures. The superficial wound edges should be closed with interrupted monofilament non-resorbable suture. Interrupted, non-resorbable sutures require removal and are less reactive then resorbable sutures. If an underlying abscess develops, individual sutures are easily removed to allow drainage without complete separation of the wound edges. Suture removal between 4 and 7 days is encouraged to prevent epithelialization of the suture tracks, decreasing the stigmata of laceration repair. Following repair, topical antimicrobials can be applied to prevent infection and promote an environment conducive to healing [25]. The use of prophylactic systemic antibiotics is controversial. It is generally agreed upon that adequately irrigated, debrided, clean wounds do not require antibiotics, while contaminated wounds especially animal bites should be treated [26, 27]. There is a lack of evidence in regards to the spectrum of antimicrobial coverage and the duration of treatment.

Conclusion

In summary, the care of pediatric craniofacial trauma patients presents a unique challenge for the entire care team, given the inherent anatomical, physiologic and psychological differences between children and adults. While a conservative approach to facial fracture management is most often needed, the clinician should maintain a high index of suspicion for concomitant injuries that may be masked on the initial exam. More invasive treatment plans should be carefully formulated given the potential for long-term effects on future growth and development from both the injury, as well as the planned operation. These considerations will ultimately lead to the best immediate and future outcome for these patients.

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Thoracic Trauma

16

Ivan M. Gutierrez and David P. Mooney

Abstract

Thoracic injuries in children are commonly the result of blunt trauma, making the diagnosis of internal thoracic injury more difficult. Unidentified injuries can cause significant morbidity and mortality and must be identified early. Injuries to the pulmonary parenchyma are the most common and the most benign. Significant injuries to the chest require a high index of suspicion, though they are rare. Understanding the major physiologic differences between children and adults is important to adequately manage children with thoracic injuries. The following review provides salient points in the recognition and management of thoracic injuries in children from blunt trauma.

Keywords

Child trauma • Thoracic injuries • Hemothorax • Pneumothorax

Incidence

Traumatic injuries are the leading cause of morbidity and mortality in children. Thoracic injuries comprise roughly 5–12 % of hospital trauma admissions in children, and are responsible for 25 % of trauma deaths in children [1]. Most thoracic injuries in children are secondary to blunt trauma, with the majority of penetrating injuries occurring in adolescents, which have a similar injury profile as adults. Isolated thoracic injuries are unusual in children and carry a 5 % mortality rate. Thoracic injuries are more often associated with head and/or abdominal injuries -and when this is the case the mortality rate rises to 25 % [2, 3].

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Anatomical and Physiological Considerations

To effectively manage thoracic injuries in children it is important to understand the anatomical and physiological differences from adults. Unlike adults, the chest wall in children is more compliant because of incomplete ossification of the ribs. This increased compliance allows energy to be transmitted to the underlying structures without any external signs of trauma or rib fractures. When rib fractures occur in childhood they become much more significant, as the application of a large force is required for them to occur. Other injuries such as commotio cordis and traumatic asphyxia are also the result of increased chest wall compliance and they will be discussed later in this chapter.

In addition, the mediastinum in children has increased mobility as compared to adults. For this reason, a tension pneumothorax may develop quickly and cause displacement of the heart and inadequate venous return, which manifests as hypovolemic shock. The physiologic response that results is more marked in a child, because their cardiac output is predominantly rate and preload dependent. The increased mobility of the mediastinum also increases the risk for tracheal deviation and this can cause respiratory compromise.

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Because the metabolic rate and oxygen consumption of children are higher than in adults, thoracic injuries increase their metabolic demand. This can be exacerbated with a concomitant pulmonary injury, which further restricts the already decreased functional residual capacity in a child. Lastly, a child's higher body surface area to weight ratio predisposes them to hypothermia, which can impede an adequate assessment of perfusion.

General Evaluation and Initial Treatment

The initial evaluation of any pediatric trauma should be a systematic approach prioritizing and establishing an airway, ensuring adequate breathing, and supporting circulation [4]. A high index of suspicion for intra-thoracic injuries should be maintained despite the absence of obvious external signs, as often physical examination is unreliable [1, 3]. Concomitant brain, abdominal, or skeletal injuries may delay the diagnosis of life threatening thoracic injuries.

Injuries to the chest can present with signs and symptoms such as nasal flaring, chest retractions or crepitus, diminished or absent breath sounds, and dyspnea. Imaging with an anterior-posterior (AP) chest x-ray is required in children with physical findings suggestive of a mechanism of injury concerning for chest injury. An AP chest x-ray will be abnormal in the majority of children with significant injuries. Markel et al. found that, compared to chest CT scan, only 5 % of 333 trauma chest radiographs failed to disclose injuries significant enough to change clinical management [5]. Similarly, Patel et al. reviewed a series of 235 children who underwent both chest radiograph and CT scan. They found that, of the 47 children found to have a pneumothorax on CT that was not seen on Chest radiograph, two of them (4 % of those with an occult pneumothorax or 1.7 % of the overall group) required a change in management [6]. CT scan of the chest is of little value in an injured child and should be reserved for a child who, based on the mechanism of injury, has concerning findings on plain radiograph (e.g. an abnormal cardiac silhouette, first rib fracture, and loss of the aortic knob) and upon clinical evaluation is thought to have suffered the rare pediatric aortic injury (Fig. 16.1).

As in adults, most thoracic injuries in children can be managed non-operatively or with a thoracostomy tube alone. Operative management is indicated for persistent hemorrhage, tracheobronchial injuries, esophageal injuries, diaphragmatic rupture, major vascular injuries, or retained hemothorax. Persistent hemorrhage is defined as loss of 20–30 % blood volume loss or ongoing hemorrhage of 2–3 ml per kilogram per hour over 4 h after thoracostomy tube placement [1, 7, 8]. A delay in operative management should be avoided as this has been shown to correlate with increased mortality in adults [9].

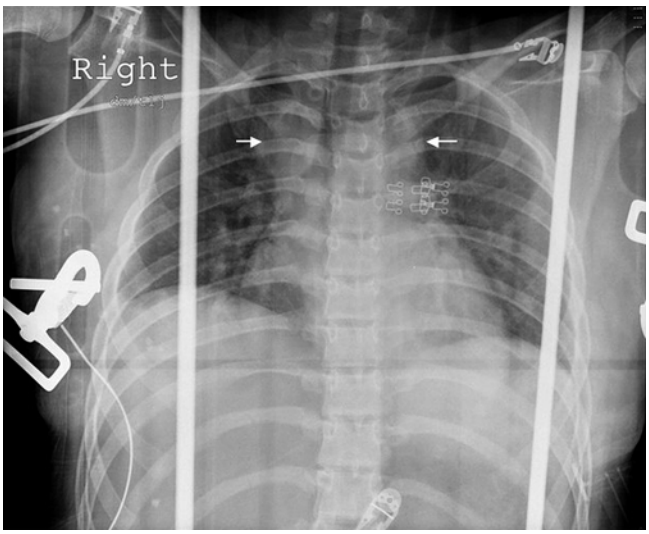

Fig. 16.1 Supine chest film demonstrating a wide mediastinum (*arrows*) and loss of the aortic knob

Specific Injuries

Bony Injuries (Rib Fractures)

Rib fractures are uncommon in children less than 3 years of age, occurring in only 1–2 % of pediatric trauma victims of that age. This can be explained by the increased compliance of the ribs, which allow bending without fracturing. Rib fractures, when they occur in isolation in young children, should raise concern for child abuse [10]. The positive predictive value (PPV) of rib fractures for non-accidental trauma in children less than 3 years is 95 %. When motor vehicle crashes or a predisposing medical condition are excluded, the PPV rises to 100 % [11]. Posterior rib fractures in a young child are pathognomonic of non-accidental injury (Fig. 16.2). In children suspected of non-accidental trauma, additional bone surveys may yield diagnostic and legal information. It should also be noted that conditions that lead to bony fragility such as osteogenesis imperfecta or rickets should be ruled out in this setting.

Rib fractures occur more frequently in older children and adolescents. Injuries to the ribs are usually diagnosed with a screening chest x-ray upon initial evaluation. Children with rib fractures have sustained a significant force to their chest and are at increased risk for an injury to the underlying organs. In addition, rib fractures may also be associated with neurologic and vascular injuries. First rib fractures in particular raise the concern for vascular injury, although the presence of mediastinal abnormalities on chest x-ray are a better indicator of intrathoracic vascular injury [12].

A flail chest is defined as multiple contiguous rib fractures with more than two points of fracture. It can lead to

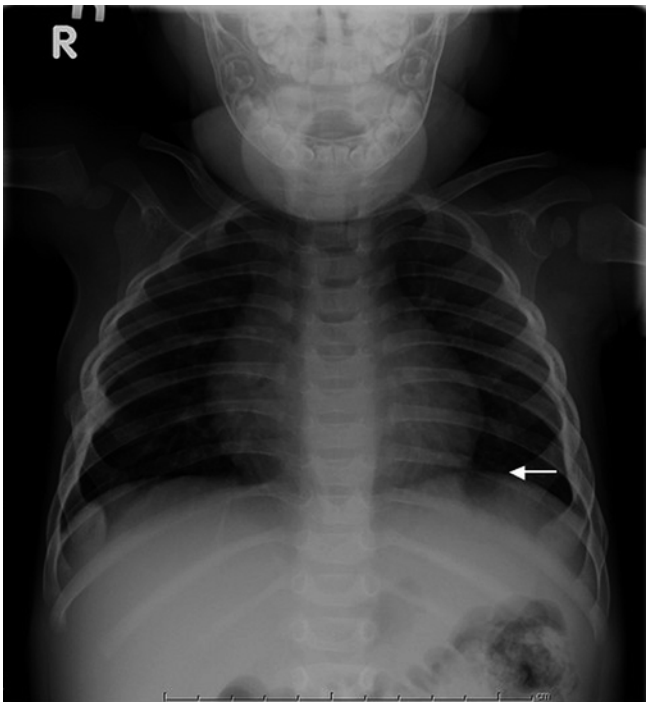

Fig. 16.2 Plain radiograph demonstrating a new posterior rib fractures (*arrow*) in the context of child abuse

respiratory compromise in children secondary to paradoxical movement of the free section of broken ribs. It is reassuring that this injury occurs in only 1–2 % of those children with rib injuries. The mainstay approach to the management of rib fractures revolves around supportive therapy. Effective pain control can be achieved with systemic or epidural analgesia. While aggressive pain therapy and pulmonary toilet are important in children, the high respiratory morbidity and mortality rate seen after rib fractures in the elderly does not occur in otherwise healthy children.

Pulmonary Injuries

Pulmonary Contusion

Pulmonary contusions are common and result from blunt trauma. In children these injuries result from motor vehicle accidents, falls, or as pedestrians being struck. The flexible chest wall in children allows for direct transmission of a blunt force to the lung parenchyma without any external signs of trauma. Pulmonary contusions result in alveolar hemorrhage, consolidation and interstitial edema at the parenchymal level.

Radiologic changes found on initial chest film include opacification and obscuration of the lung parenchyma. In 67–90 % of children with clinically significant pulmonary contusions, the initial chest x-ray is abnormal, however plain film imaging which is read as normal does not exclude the diagnosis [1]. Pulmonary contusions that are noted incidentally on computed tomography upper cuts of the abdomen but not on plain film are subclinical, do not require follow up or change in management and do not comprise an indication for CT scan of the chest [6].

The clinical presentation of pulmonary contusions varies, ranging from simple abnormalities seen on chest x-ray without symptoms to severe respiratory distress. Complications of pulmonary contusions include pneumonia, acute respiratory distress syndrome (ARDS), and death [13]. Mechanical ventilation is used less for pulmonary contusions in children than in adults. Approximately 20 % of children with significant pulmonary contusions will develop pneumonia. ARDS occurs in 5–20 % of cases, with death from this injury being extremely rare in children [13, 14].

Treatment of children with pulmonary contusions is supportive and includes pain control, supplemental oxygen, and excellent pulmonary toilet. In addition, prevention of atelectasis by encouraging ambulation and avoiding long general anesthetics is important. With appropriate management nearly all children improve within 2–5 days.

Pneumothorax/Hemothorax

Pneumothorax and hemothorax occur in children as the result of mechanisms with significant energy transfer: motor vehicle crashes, falls from height, and pedestrians struck. The increased compliance of the chest wall and mobility of the mediastinum in children puts them at increased risk of cardiovascular collapse with these injuries. Therefore, it is necessary to make a prompt diagnosis to ensure appropriate management. Chest imaging with plain films can demonstrate the presence of air or blood in the pleural space. Computed tomography of the chest is usually not necessary and the pneumothoraces and hemothoraces seen on CT scan but not on plain film are subclinical and a conservative approach without intervention is advocated [15].

With a significant pneumothorax, the goal of treatment is to evacuate the air from the pleural space and avoid mediastinal collapse, as would occur with a tension pneumothorax. In a child that is unstable, the evacuation of air should not wait for the placement of a thoracostomy tube, and an anterior needle thoracostomy should be performed, as in adults. In general a traumatic pneumothorax will also contain some blood, so the caliber of the chest tube used should be sufficient to evacuate air and blood, as smaller tubes may become occluded over time (Table 16.1).

The most common sources of blood in the pleural space are lacerated intercostals vessels, and parenchymal lacerations. In younger children with flexible chest walls lacerated intercostal vessels are less common. A large volume hemothorax can also be indicative of a great vessel injury [3]. After diagnosis, blood should be evacuated from the pleural space with tube thoracostomy to avoid the complications of empyema or fibrothorax.

Table 16.1 Suggested chest tube sizes by patient weight

Weight, kg	Chest tube size, Fr
3–5	10–12
6–9	12–16
10–11	16–20
12–14	20–22
15–18	22–24
19–22	24–28
23–30	24–32
>32	32–40

Adapted from Bliss and Silen [3]. With permission from Lippincott Williams & Wilkins
kg kilogram, *Fr* French

Tracheobronchial Injury

Injuries to the tracheobronchial tree often pose major diagnostic and therapeutic challenges. Tracheobronchial injuries occur in 0.7–2.8 % of children with blunt chest trauma. The mortality of these injuries has been reported to be as high as 30 %, with most of the deaths occurring within the first hour after injury [1, 16, 17]. The majority of these injuries occur in the membranous back wall of the trachea and mainstem bronchi within one inch of the carina and are the result of a compression force between the sternum and the spine [1]. In addition, tracheobronchial injuries can result from a "tracheal blast" which occurs when intratracheal pressure rises rapidly against a closed glottis [18].

Associated radiographic findings include cervical subcutaneous emphysema, air in the mediastinum, pneumothorax, or hemothorax. Clinically, these injuries may present with signs and symptoms consistent with a tension pneumothorax. One hallmark of this condition is the presence of a persistent continuous air leak following the placement of a tube thoracostomy for a pneumothorax. Imaging modalities of the chest rarely demonstrate a clear disruption of the trachea or bronchus [17]. Bronchoscopy may be used for diagnosis and localization of injuries and allows for placement of endotracheal tubes distal to the injury for ventilation when necessary [19].

Relatively small injuries of the trachea in a stable child can be managed with thoracostomy tube alone [20]. Surgical management is warranted for significant tracheobronchial injuries. Preoperatively, if possible, endotracheal tubes should be placed distal to the injury to facilitate repair and provide adequate respiratory support. Complications associated with surgical repair include bronchopleural fistula and bronchial stenosis. The management of these complications is beyond the scope of this review.

Traumatic Asphyxia

Traumatic asphyxia is an unusual condition and is the result of sudden and severe compression of the chest resulting in the transmission of high venous pressures to the upper body. The classic clinical presentation is: facial edema, cyanosis, and petechial hemorrhages of the face, neck, and chest. Traumatic asphyxia may be associated with other injuries such as pneumothorax, hemothorax, flail chest, and abdominal injuries. Supportive management and appropriate treatment of associated injuries typically yields a positive outcome [21, 22].

Mediastinal Injuries

Blunt Aortic Injury

Injuries to the great vessels are rare in children but, when they do occur, the mortality is high. Prompt diagnosis and expeditious treatment are required to improve survival [23]. Injuries to the thoracic aorta were found at autopsy in 2–5 % of children dying from blunt trauma compared to 15–17 % of adults [1]. The majority of blunt aortic injuries (BAI) occur in boys with a mean age of 12 years. Up to 80 % of children with BAI have concomitant injuries to the lung, heart, long bones, and abdominal viscera [24]. The injury most commonly occurs at the ligamentum arteriousum. The mechanisms associated with BAI are the same high-energy mechanisms that lead to a pneumothorax or hemothorax: motor vehicle collisions, pedestrian impacts, and falls from significant height.

The diagnosis of BAI can be difficult because of their rarity. Physical exam findings that may raise suspicion for BAI include associated first rib fractures, sternal fractures, paraplegia, upper extremity hypertension, and lower extremity pulse deficits [1, 23]. Chest x-ray may demonstrate widening of the mediastinum, loss of aortic knob, deviation of the esophagus (noted in children with a nasogastric tube in place), and first rib fractures. Seven percent of patients with BAI have a normal chest x-ray [25]. A chest x-ray suggestive of BAI with a concerning mechanism should prompt evaluation with helical computed tomography (Fig. 16.3), which has replaced arch aortography as the gold standard [25, 26].

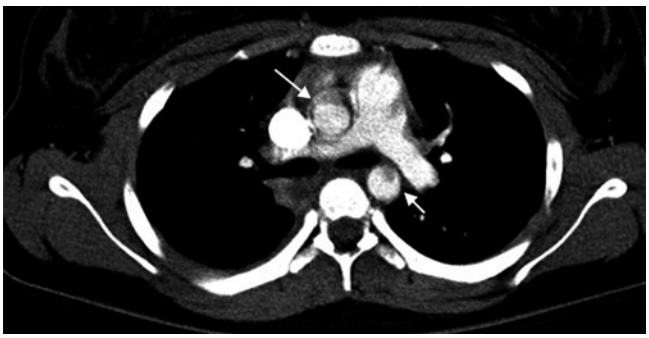

Fig. 16.3 Chest CT demonstrating proximal ascending and descending aortic injury associated with a pseudoaneurysm (*long arrow*)

In children with BAI, beta blockade should be initiated to minimize shear forces on the aortic wall and minimize the chance of rupture. The optimal management strategy of this rare injury remains uncertain. Most children undergo thoracotomy and repair of their BAI. In children with concomitant injuries that preclude thoracotomy, expectant management or endovascular repair have been successful. Serial helical CT scans and strict blood pressure control with a target systolic blood pressure of 120 mmHg or 20 mmHg less than baseline are required when expectant management is employed [25–27]. Endovascular repairs have been successful in adults, however there is limited experience in children [27, 28]. It is important to note that open primary surgical repair is preferred over vascular grafts to avoid aortic pseudocoarctation as the child grows [23, 27].

Blunt Cardiac Injury

Blunt cardiac injury is the term used to describe a spectrum of conditions, which include myocardial contusion, rupture of cardiac chambers, and disruption of cardiac valves. These injuries are unusual in children with an incidence of 0.3–4.6 %. In children, myocardial contusions are the most common and account for 95 % of these injuries [29].

Myocardial contusions are difficult to diagnose and can be manifested as dysrhythmias and hypotension. The evaluation of children with suspected myocardial contusion includes an electrocardiogram (ECG) and cardiac enzymes. An ECG may be diagnostic if there are abnormalities, but is not uncommon for it to be normal. Troponin I has been found to be more sensitive for diagnosing cardiac contusions [3]. In the setting of child with a history of chest trauma and unexplained hypotension it is recommended to obtain an echocardiogram which might demonstrate hypokinesis or ventricular wall motion abnormalities [30].

The management of myocardial contusions is largely supportive. Children should be admitted for continuous cardiac and hemodynamic monitoring. In our experience, the length of stay in the hospital is determined by the time that it takes for cardiac enzymes to normalize and for rhythm disturbances to resolve. In patients with persistent dysrythmias and hypoperfusion, inotropes should be used carefully because they increase myocardial oxygen consumption. If operative management is required for a concomitant injury, careful selection of anesthetic agents is recommended to avoid myocardial depression. Most children with myocardial contusions will improve with expectant management and will have limited long term sequelae [29].

Commotio Cordis

Commotio cordis is unique in pediatric thoracic trauma. In occurs in children as a consequence of a direct blow to the chest and may result in sudden death [31]. It is frequently associated with participation in competitive sports such as baseball, hockey, and lacrosse where a dense object (i.e. ball) can become projectile. The diagnosis is made based on the clinical presentation and electrocardiographic data demonstrating ventricular fibrillation in the absence of acute myocardial contusions and cardiac structural anomalies. The primary mechanism described for sudden death from commotio cordis is an external impact that occurs during a vulnerable moment of the repolarization period, which induces ventricular fibrillation [32]. Rapid recognition of this entity and prompt defibrillation can be life saving.

Esophageal Injuries

Injuries to the esophagus from blunt abdominal trauma are rare, because it is relatively well protected in the thorax. When esophageal injuries occur they are typically associated with other injuries. Esophageal injuries may present as unexplained mediastinal air, pleural effusions, fever, sepsis, and chest or epigastric pain.

Suspected injuries should be evaluated with a water-soluble contrast esophagram and rigid esophagoscopy. If an injury is found, management will vary depending on location and size of injury. Broad-spectrum antibiotics and fluid resuscitation should take precedence prior to any surgical repair. Treatment options include non-operative management, esophageal primary repair, esophageal exclusion and diversion [33]. Non-operative management should be reserved for patients with a contained esophageal perforation and with no evidence of mediastinitis. In a child with evidence of mediastinitis, exclusion of the esophagus as well as drainage of the mediastinum is the correct treatment. In children primary surgical repair is preferred and possible in most cases.

Pneumomediastinum

The presence of pneumomediastinum (Fig. 16.4) raises concern for significant injuries, such as esophageal or tracheal perforations. Approximately 90 % of adults noted to have pneumomediastinum on evaluation, however, are asymptomatic [34]. In clinically stable, asymptomatic children, the value of triple endoscopy and/or extensive imaging studies to rule out an esophageal or tracheal injury has been called into question [35, 36]. Investigation for the source of mediastinal air should be limited to symptomatic patients or those with other significant thoracic injuries.

Diaphragm

Blunt chest trauma results in diaphragmatic rupture in 1–2 % of children with thoracic injuries. The left hemidiaphragm is involved in two thirds of cases with the posterolateral position being the most frequent location [3]. Given its proximity to the abdominal solid organs, most cases of diaphragmatic rupture are associated with injury to the

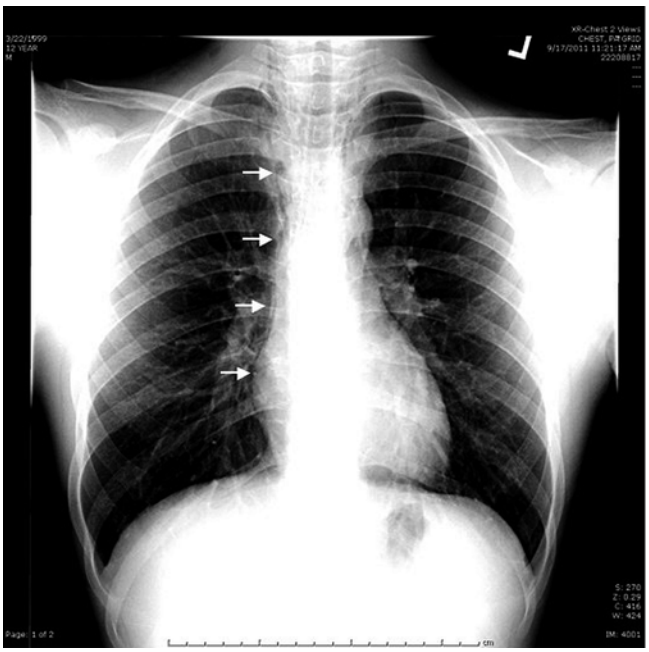

Fig. 16.4 Chest x-ray of a 12-year-old male with air in the mediastinum (*arrows*)

kidneys, liver or spleen [37]. Patients with diaphragmatic rupture are at increased risk for intestinal or organ herniation, which can lead to strangulation if the injury is not diagnosed readily [38].

The diagnosis of diaphragmatic rupture remains challenging, as often it is difficult to separate signs and symptoms of diaphragmatic injury from concomitant injuries. Patients may complain of respiratory distress and chest pain. Physical examination may reveal decreased breath sounds or bowel sounds in the affected side. Chest x-ray demonstrates the diaphragmatic injury in 25–30 % of injured patients and a normal chest x-ray does not rule out the diagnosis [39]. Signs found in chest x-ray include an abnormal diaphragmatic contour, a bowel gas pattern in the chest or a nasogastric tube coiled in the hemithorax. Computed tomography has been used to establish the diagnosis, however only has a sensitivity of 33–83 % and a specificity of 76–100 % [38]. One advantage of CT scan is that it allows for evaluation of other structures in the abdomen. Other modalities have been used to diagnose diaphragmatic injury including enteral contrast studies, fluoroscopy, and ultrasound. However, when there is significant suspicion on imaging a laparoscopy, laparotomy, or thoracoscopy is warranted [40, 41].

Emergency Room Thoracotomy

The use of resuscitative thoracotomy has been extensively reviewed in the adult population, however its use in children still remains a controversial topic. There is no data to suggest that emergency thoracotomy has a more favorable outcome in children than in adults. In fact, the outcomes in children seem to mirror those in adults with a survival based on mechanism; with only 2 % of patients surviving after blunt injury. The best survival rates are for those patients with isolated penetrating injury and range between 20 and 35 % [42, 43]. The current indications for emergency room thoracotomy guidelines provided by the American College of Surgeons are the same for both pediatric and adult patients (Table 16.2) [44]. Resuscitative thoracotomy is not indicated in pediatric patients presenting to the emergency room without measurable vital signs after blunt trauma as they are deemed non salvageable.

Table 16.2 Indications for emergency room thoracotomy

Patients sustaining penetrating injuries with objectively measurable physiologic parameters
Patients sustaining exsanguinating abdominal vascular injuries as an adjunct for definitive resuscitation and repair of the abdominal injury
Patients that experience a witnessed cardiopulmonary arrest and arrive in emergency room with vital signs

Adapted from Working Group, Ad Hoc Subcommittee on Outcomes, American College of Surgeons-Committee on Trauma [44]. With permission from Elsevier

Summary

Blunt thoracic trauma is a major contributor to injury morbidity and mortality in children. Thoracic trauma may result in a wide array of injuries that must be diagnosed promptly. Once diagnosed, a thorough understanding of pediatric physiology is important to effectively manage these conditions. The clinician's responsibility is to effectively diagnose, prioritize and treat common thoracic injuries, while maintaining a high index of suspicion for potentially devastating unusual injuries.

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Abdominal Trauma

17

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and Ivo de Blaauw

Abstract

Abdominal trauma in children is relatively uncommon but may be associated with considerable morbidity and mortality. Further damage should be prevented by optimal evaluation of specific anatomic features that make the injured child more susceptible for solid organ injuries. The spleen is the most frequently injured intra-abdominal solid organ. The liver is the second most injured organ in children. The management of both spleen and liver injuries in children is predominantly non-operative; laparoscopy or laparotomy is only performed in hemodynamic unstable patients and in those with a hollow viscus perforation. Non-operative management of isolated spleen and liver injury in a pediatric trauma center can be successful in more than 95 % of cases. Pancreatic injuries are more difficult to diagnose on both CT scan and with laboratory findings. Treatment options vary by type of injury and surgeons' preferences. Contusions are mostly treated non-operatively; pancreatic transections (grade III injuries) are treated operatively in some centers and non-operatively in other centers. Endoscopic treatment has become first choice of treatment for pancreatic transections in a few centers provided the pediatric gastroenterologist has the required skills. Hollow viscus injury is the relatively rarest kind of injury. Its diagnosis is still a major challenge and is often delayed. Treatment is similar as to that in adults with the resection of the involved bowel and/or mesentery. Finally, penetrating abdominal trauma accounts for approximately 10 % of abdominal trauma in children and has a high mortality rate, particularly in the very young ones. In conclusion, abdominal trauma in children is rare and both nonoperative treatment and emergency surgical treatment should be adapted to the type of injury of the intra-abdominal organs involved.

Keywords

Pediatric trauma • Spleen • Liver • Pancreas • Intestine • Abdominal compartment syndrome • Blunt trauma • Penetrating trauma

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Introduction

Trauma is the leading cause of death and disability in children in the developed world. While head and thoracic injuries are the leading causes of trauma-related death in children, intra-abdominal injuries carry considerable morbidity and can be fatal in children if not recognized early [1]. Abdominal trauma affects approximately 10–15 % of injured children. In pediatrics, abdominal injury is due to blunt forces in 90 % of cases, while only 10 % are due to penetrating injury.

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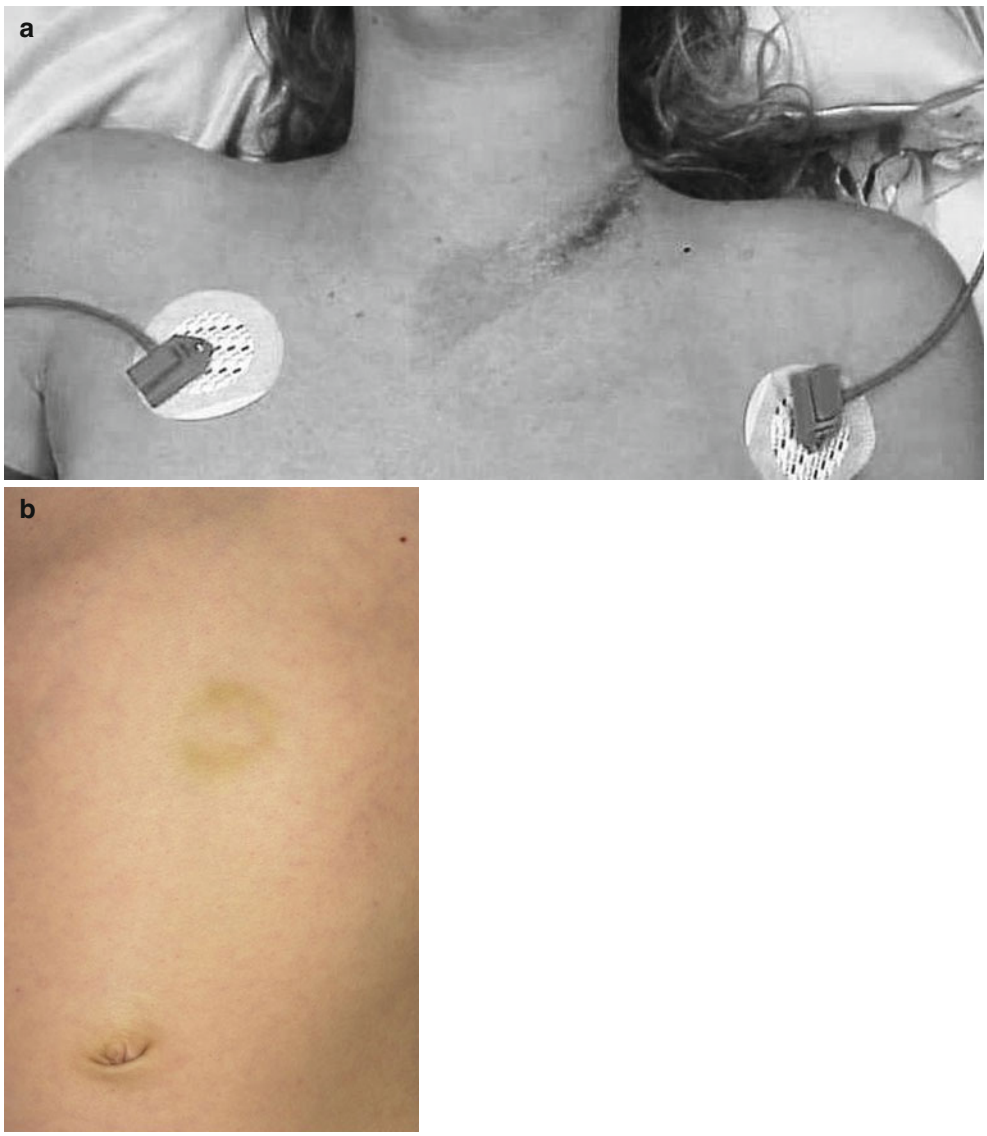

Fig. 17.1 Physical examination reveals several typical signs in pediatric abdominal trauma. (**a**) Seatbelt sign; (**b**) Handlebar injury

Mortality is higher in blunt abdominal injury [2], which may be related to the fact that approximately 40 % of children with blunt abdominal trauma have associated injuries. Falls and traffic related crashes are the most common etiology of abdominal trauma in children [2, 3].

Several key anatomical properties make children more prone to abdominal injury. First, the traumatic forces and energy are distributed over a smaller body size. Therefore, the number of systems injured during trauma is likely to be higher. Second, the ribs are elastic and give little protection to internal organs like the liver and spleen. Ribs can be completely compressed without fracturing but the compression may still result in severe liver or spleen injury. Fractured ribs always point at severe trauma [4]. Third, the diaphragm has an almost horizontal orientation and is flatter and less dome-shaped than that of adults, which pushes the spleen and liver below the rib cage where they are more prone to injury. Fourth, the solid organs are also relatively larger than in adults [5]. Finally, the abdominal wall is relatively underdeveloped and has little insulating fat. The abdominal wall thus has little resistance to incoming forces and gives less protection to abdominal organs.

Initial Evaluation of the Child with Suspected Abdominal Injury

All trauma patients should be managed by the principle of "treat first what kills first". The initial evaluation of a child with abdominal trauma should consist of a primary survey, following the Advanced Trauma Life Support guidelines from the American College of Surgeons [6]. Following the initial primary survey, a more detailed examination of the abdomen should be performed. Cutaneous manifestations of underlying abdominal injury include bruising, excoriation, or asymmetric movement of the abdominal wall musculature. For example, the so-called "seat belt sign" (Fig. 17.1) should raise the index of suspicion for underlying abdominal injury (or thoracic injury) [7]. Badly positioned lap belts, e.g.

positioned over the immature iliac crest, can cause severe injury by migrating onto the abdomen during rapid deceleration, especially in children between 4 and 9 years. Typical injuries associated with the seat belt sign include small bowel contusions, lacerations or perforations, lumbar flexion and distraction injuries with spinal cord lesions [8, 9]. Other possible injuries include mesenteric hematomas, rupture of bladder and diaphragm, and vascular injuries [10]. Small children easily swallow air and the resultant gastric distension may cause respiratory failure and aspiration. Feeling and palpating the abdomen helps to guide any further investigations as abdominal pain and tenderness are both very suggestive for localized intra-abdominal injury in children [11].

If the child is hemodynamically stable, further diagnostic evaluation can be performed, including laboratory testing and radiologic evaluation. During the primary survey, a CBC with blood-type determination and cross-match should be obtained. While of limited value for the purposes of identifying occult abdominal injury in children [2, 12, 13], additional laboratory tests often include a urinalysis, complete blood count, serum electrolytes, blood glucose, liver aminotransferases, amylase and lipase, blood gas analysis, and coagulation studies.

Microscopic and/or macroscopic hematuria is highly suggestive of intra-abdominal injury – but not necessarily of renal injury [14, 15]. Although macroscopic hematuria is more predictive for renal injury it only has a positive predictive value up to 22 % [13]. In general, >50 red blood cells per high power field on urinalysis warrants further investigation for intra-abdominal injuries [16]. On the other hand, severe renal trauma (renal pedicle injury or isolated urethral injury) can also be present in the absence of hematuria.

The white blood count is elevated in every trauma patient and has no specific role in the initial evaluation. Electrolyte abnormalities are seldom observed in acute trauma patients [17]. However, measurement is highly relevant in cases of large blood loss, shock, and metabolic acidosis with disturbed electrolyte metabolism. Blood glucose may be elevated in the setting of acute stress.

Several studies have shown that higher levels of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) in combination with abnormalities found on physical examination are predictive for abdominal injury [11, 18]. However, these elevations mostly do not differentiate between different organs. As an exception, liver transaminase levels exceeding 250–400 U/L correlate with liver injury with a high positive predictive value [19]. Amylase and lipase levels are usually elevated in any pediatric trauma patient. Conflicting findings on the value of elevated amylase and lipase levels for the prediction of pancreatic injury have been reported. For example, one study found a correlation between elevated amylase or lipase levels and the severity of the pancreatic injury [20], whereas another did not [21]. Furthermore, some studies have found normal serum values in patients with severe pancreatic injury [22, 23]

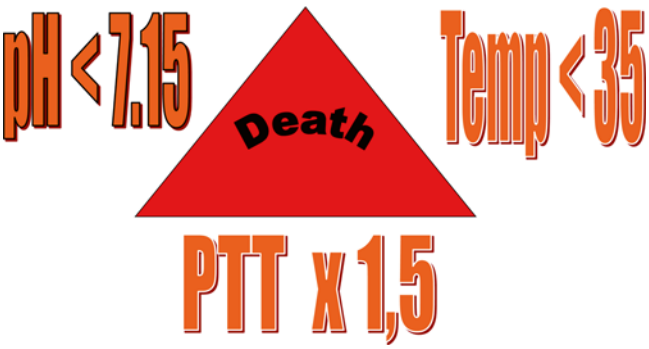

Fig. 17.2 Triangle of death: metabolic acidosis, hypothermia and coagulopathy. The triangle of death symbolizes the three parameters to strictly monitor in severe trauma patients. When these three parameters deteriorate damage control surgery is warranted to rapidly stabilize the patient

Routine coagulation studies in previously healthy children are seldom necessary [24]. However, they are recommended in case of shock. Coagulation disorders are part of the "triangle of death"-formed by three physiological dearrangements: hypothermia-metabolic acidosis-coagulopathy (Fig. 17.2) [25]. When these occur simultaneously the patient will enter into an irreversible shock which ultimately leads to death. Any definitive surgical correction is then futile. Staying ahead of these dearrangements is essential and is achieved by "damage control surgery." This means that any bleeding must be stopped immediately, that further contamination must be prevented and that the child must be transferred as soon as possible to the pediatric intensive care unit (PICU) to stabilize metabolism. Rapid hemostasis is best achieved by packing the liver, spleen and if necessary the entire abdomen. Further contamination is prevented by resection of perforated or necrotic bowel with tying of the ends or closure with clips or stapler devices. It is not necessary to anastomose the bowel or construct stomas. Bowel continuity is restored in a subsequent laparotomy after stabilization at the PICU. The abdomen is temporarily closed, either by towel clips, skin only closure, prosthetic material sutured to fascial edges or vacuum assisted closure devices. After this, the patient returns to the PICU for resuscitation and stabilization. The goals are rewarming, correction of coagulopathy and reversing the metabolic acidosis. This critical stage of damage control may take long and can be complicated. If the child's condition has stabilized a second look laparotomy is performed for pack removal, debridement and definitive repair [25].

Imaging

A computed tomography (CT) scan has been the gold standard for the evaluation of blunt abdominal trauma for many years. Plain abdominal X-ray is hardly ever used except

occasionally to detect extraluminal intra-abdominal free air in hemodynamically normal and stable patients. In patients with penetrating trauma it may serve to determine the track of the missile using paperclips at the entrance and exit points. Ultrasound scanning (US) is extensively used in pediatrics because of its non-invasive nature and lack of radiation exposure. Focused Abdominal Sonography for Trauma (FAST) is an established method for the screening of abdominal injuries in adults [26] and has almost completely replaced the diagnostic peritoneal lavage procedure [27]. The sensitivity of FAST in children is relatively low, though the specificity is high [28, 29]. Therefore, if US shows free intraperitoneal fluid in children, the chance of organ injury is high; however, many children with severe organ injury are without free intraperitoneal fluid [29]. US does not differentiate between type of organ injury and therefore many pediatric trauma surgeons consider the presence of free fluid on US irrelevant [30]. However, when used in the pediatric trauma room, a positive US examination is indication to perform further investigations.

CT scan is the method of choice in most hospitals for the evaluation of abdominal injury after blunt trauma in hemodynamically stable children. It allows accurate detection of hepatic, spleen, adrenal and renal injuries. It further provides useful information on the severity of injury, the involvement of the organ's blood supply and any vascular injury [31, 32]. CT scans still have limited value for pancreatic, intestinal, mesenteric, diaphragmatic and bladder injury [33–35]. But then again, the overall rate of intra-abdominal injury is very low (0.19 %) after a negative CT scan in children [34]. For a good result, intravenous contrast is essential to distinguish hematoma from solid viscera or to detect active hemorrhage. There is controversy regarding the use of oral contrast after blunt trauma. Potential benefits may be enhanced detection of small intramural or mesenteric hematomas, improved delineation of pancreas from surrounding bowel, and detection of contrast extravasation. The major downsides of oral contrast are longer scanning time, more nasogastric tubes needed, vomiting and aspiration of contrast [36].

The major drawback of a CT scan is the exposure to a high dose of ionizing radiation, which may pose future health risks for children. The dose received from a whole body CT-scan is 100–1,000 times the dose delivered by conventional radiographs and varies between 17 and 90 mSv [37]. For 3-year-old children the mean life time cancer risk has been approximated at 1 in 150 in girls and 1 in 300 in boys. In comparison, for adults it is estimated to be 1 in 1,500 after a similar CT scan. Considering that 50–80 % of the CT scans in pediatric trauma patients show no abnormalities indicates that we need to find a better indication for a CT scan [37]. A recent study proved that repeated US guided appropriate surgical treatment in 97 % of pediatric trauma patients without any need for CT scans [38].

Magnetic resonance imaging (MRI) of the abdomen is little used in trauma care. It is time consuming and often requires anesthesia and intubation to keep the child immobile. MRI is almost only used to evaluate spinal cord injury. Diagnostic peritoneal lavage is also little used in pediatric trauma and has mostly been replaced by US.

Laparoscopy is becoming more common to avoid laparotomy when intra -abdominal injury is suspected but cannot be confirmed by CT [39–41]. Injuries that are hard to detect on CT scan, such as diaphragmatic injuries, can also easily be seen. Laparoscopy furthermore enables the repair of minor injuries of parenchymal organs and diaphragm [42]. However, it still remains an invasive diagnostic tool with possible complications and is not fully reliable. For example, hollow viscus perforations and retroperitoneal injury are still often missed and misdiagnosed. Still, in case of proven lesions of the gastrointestinal tract, conversion to laparotomy is considered mandatory in most trauma centers [43]. However, in some centers the availability of skilled minimal invasive surgeons may result in the use of laparoscopy in the management of intra-abdominal injuries with good clinical outcome [44].

Specific Organ and Tissue Injuries

Management of most solid organ injuries in children is predominantly non-operative. In recent years this approach has even become the standard in adult abdominal (spleen, liver) trauma as well [45, 46]. The major reason for a surgical intervention in pediatric blunt abdominal trauma is hemodynamic instability or suspicion of a hollow viscus perforation. Specific organ injuries and treatment options are discussed below.

Spleen

The spleen is affected in nearly one-third of all pediatric intra-abdominal injuries. Costal fractures in adults are commonly associated with splenic injury, though rib fractures are present in children only in 10 % of cases. Solitary splenic injury has limited signs and symptoms – patients are hemodynamically stable, with symptoms of mild to moderate blood loss. They have local pain in the left upper quadrant, and referred pain in the shoulder. Comorbidity that increases the size of the spleen (e.g. mononucleosis, lymphoproliferative disorders) predisposes patients to rupture, even with low energy trauma. US can diagnose free fluid intra-abdominally, as a sign of splenic injury. However, 15–40 % of splenic injuries are missed, since a blood clot has a similar aspect on US as splenic tissue. CT scan of the abdomen with intravenous contrast is the gold standard to diagnose and grade splenic injury. Classification is according to the system proposed by the American Association for the Surgery of Trauma [47] (Table 17.1).

Table 17.1 Splenic injury scaling system with grading according to American Association for the Surgery of Trauma (AAST)

Grade 1	Subcapsular hematoma, <10 % of surface
	Capsular laceration <1 cm deep
Grade 2	Subcapsular haematoma 10–50 % of surface area
	Intraparenchymal haematoma <5 cm in diameter
	Laceration 1–3 cm depth not involving trabecular vessels
Grade 3	Subcapsular haematoma >50 % of surface area or expanding
	Intraparenchymal haematoma >5 cm or expanding
	Laceration >3 cm depth or involving trabecular vessels
	Ruptured subcapsular or parenchymal haematoma
Grade 4	Laceration involving segmental or hilar vessels with major devascularization (>25 % of spleen)
Grade 5	Shattered spleen
	Hilar vascular injury with devascularised spleen

Adapted from Moore et al. [47]. With permission from Wolter Kluwers Health

Table 17.2 Management algorithm after splenic injury according to the protocol of the APSA Liver/Spleen Trauma Study Group

	Grade I	Grade II	Grade III	Grade IV
ICU (days)	0	0	0	1
Hospital stay (days)	2	3	4	5
Predischarge imaging	None	None	None	None
Postdischarge imaging	None	None	None	None
Activity restriction (weeks)	3	4	5	6

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More than 95 % of pediatric splenic injuries are treated non-operatively in pediatric trauma centers. If operation is opted for, it is done within the first 24 h in almost 90 % of cases. Recurrent bleedings are unlikely after 48 h. It is recommended to observe the child for a certain period, depending on the grade of injury which has been validated for safety in a multicenter study [3]. An example of a management algorithm is provided in Table 17.2. After a maximum of 6 weeks all splenic injuries are considered to be healed and activity restriction can be abandoned. There is no need to further monitor the condition of the spleen with further CT or US before or after discharge.

Some controversy still exists concerning the event of a contrast blush seen on the initial CT scan. In that case, most patients can still be managed non-operatively but failure of non-operative management is described in approximately 20 % of these cases, which is considerably higher than the overall rate of failure of non-operative management [48, 49]. The role of angiographic embolization still remains to be determined; most pediatric trauma centers have little experience with this method.

Applying specific treatment guidelines in dedicated pediatric trauma units reduces the risk for surgery by two to threefold [50]. The decision for surgical intervention is made based on hemodynamic instability and blood requirements. Surgically treated splenic injury in children requires simple packing, splenorraphy or partial splenectomy. Several cases of laparoscopic splenic repairs have been successful but hemodynamic instability often warrants a rapid emergency laparotomy with the least loss of time. Splenectomy is usually only required for polytraumatized patients when any splenic repair is too time consuming and rapid splenectomy is performed for stability. After splenectomy the incidence of overwhelming postsplenic infection is low, but mortality is still high at 50 %. Postoperative immunization is required with polyvalent vaccines against encapsulated gram positive organisms, e.g. *Hemophilus influenza* type B, pneumococci, and meningococci. In addition daily prophylaxis of with penicillin is recommended until the age of 12 years. The risk of long term complications of non-operative management of splenic injuries in children is very low. Pseudocysts and pseudoaneurysms following splenic injury have incidentally been reported and are estimated to occur in less than 0.4 %. Again, this justifies abandoning any diagnostic follow up [51, 52].

Liver

Although the liver is a bigger organ than the spleen, it is less frequently injured in blunt abdominal injury. One-third of the pediatric liver injuries are solitary. In penetrating injury, however, the liver is the most frequently injured solid organ. Liver tissue is more elastic than splenic tissue, which may account for a greater resistance to force. Liver injuries are generally more severe than spleen injuries and are the most common lethal abdominal injury. Symptoms of liver injury can vary from mild to severe abdominal pain, referred pain in the right shoulder, mild to severe shock and liver enlargement due to subcapsular hematoma formation. Consistent with splenic injury, US can detect free intra-abdominal fluid and is suggestive for liver injury if found around the liver (in Morrison's pouch), but cannot adequately confirm or exclude injury. CT scan with intravenous contrast is always indicated.

Grading of liver injury is also according to the organ injury scaling system of the AAST (Table 17.3). Solitary liver injury can be treated following the same algorithm as in splenic injury (Table 17.2). In about 90 % of the cases non-operative treatment is possible, especially in grade I-IV injury [53, 54]. In higher grade injuries the probability of requiring surgery is greater but an initial attempt at non-operative treatment is always warranted. Resuscitation and prevention of hypothermia are essential. If coagulation disorders are present, fresh frozen plasma, platelets, and cryoprecipitate are administered. Laparotomy is indicated in grade V–VI liver

injury with refractory hypotension or persistent bleeding after initial stabilization. Selective arterial embolisation may be attempted if the patient has stabilized and an arterial blush is seen on CT scan. However, in (small) children experience is limited and in most cases a laparotomy is performed.

There are two techniques to rapidly control liver bleeding [55]. The first is the Pringle maneuver in which the common hepatic artery and portal vein are gently clamped to diminish active bleeding. This often gives the opportunity to assess the extent of injury. In young children the sternum can be divided rapidly to expose the suprahepatic or infracardial inferior caval vein, allowing for a total hepatic isolation. Children can tolerate vascular isolation of the liver for 30 min or longer. Definitive control of severe liver injury can then be achieved with manual compression, direct suture ligation, topical hemostatic agents or fibrin glue and mesh wrapping. The second possibility is to pack the liver (with very limited mobilization) from all sides. These maneuvers control hemorrhage in more than 95 % of cases. After temporary abdominal closure, liver packing allows to make further choices to try to embolize bleeding arteries or to consider a partial liver resection after demarcation. Again, complications of non-operative management of liver injury are very rare but include rarities such as hemobilia, biliary leaks and biliary peritonitis, subphrenic abscesses, liver necrosis and portal venous thrombosis. Complication rates are consistently higher in case of operative management [55].

Table 17.3 Liver injury scaling system with grading according to American Association for the Surgery of Trauma (AAST)

Grade 1	Subcapsular hematoma, <10 % of surface Capsular laceration <1 cm deep
Grade 2	Subcapsular haematoma 10–50 % of surface area Intraparenchymal haematoma <10 cm in diameter Laceration 1–3 cm depth, <10 cm in length
Grade 3	Subcapsular haematoma >50 % of surface area or expanding Intraparenchymal haematoma >10 cm Laceration >3 cm depth
Grade 4	Laceration 25–75 % of liver lobe Laceration 1–3 Couinaud segments
Grade 5	Laceration >75 % of liver lobe Laceration >3 Couinaud segments within a single lobe Juxtahepatic venous injury, i.e. retrohepatic vena cava or central major hepatic veins
Grade 6	Hepatic avulsio

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Pancreas

Pancreatic injury is relatively rare in children: 3–12 % after blunt and penetrating trauma. The main mechanism of injury is a bicycle accident with impalement of the bicycle handlebar (Fig. 17.1b). Patients present with epigastric pain, often with a delay of 24–48 h. Physical examination often reveals minimal or no abdominal findings. Elevated amylase or lipase levels are indicative but not specific since these may occur as well with facial injury or bowel injury. CT imaging is the diagnostic technique of choice but the early positive predictive value of pancreatic trauma in children is low. Edema and fluid collections mostly appear after 24 h and this increases the sensitivity of CT enormously. The grading is according to the Organ Injury Scaling Committee of the American Association for the Surgery of Trauma. Grade I and II are minor and major contusions, grade III is a pancreatic corpus transection (Fig. 17.3a), grade IV is a more proximal transection at the pancreatic head, grade V is a complete transection of the pancreatic head (Table 17.4). If a pancreatic duct injury

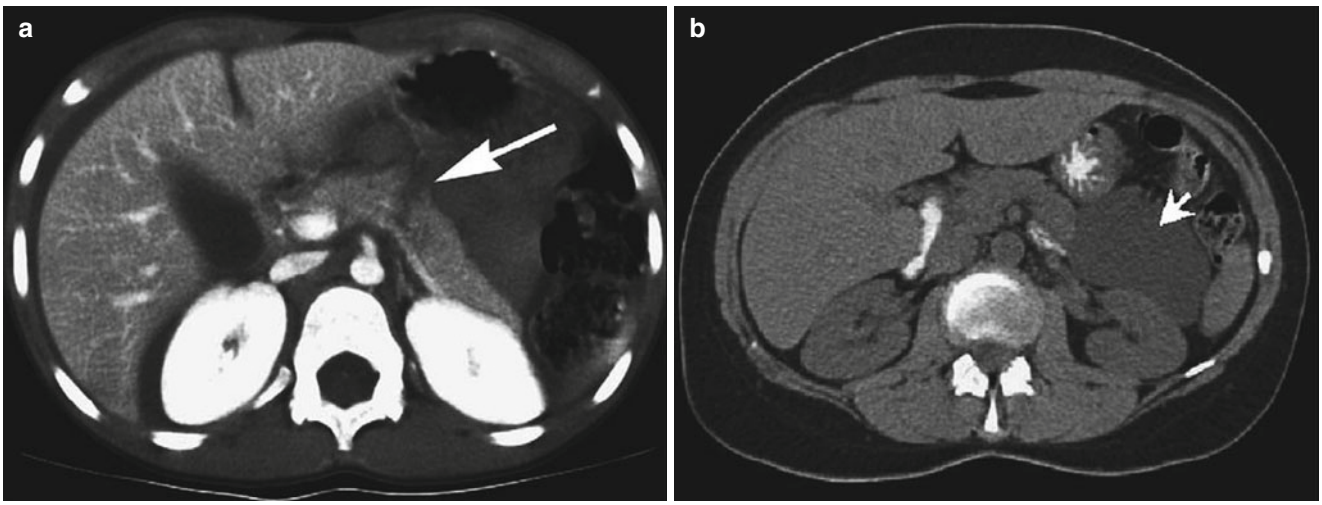

Fig. 17.3 (**a**) Grade III pancreatic injury. The *white arrow* points at the ruptured corpus of the pancreas. (**b**) Pseudocyst at the tail of the pancreas (*white arrow*). The pseudocyst was formed 6 weeks after the initial trauma. It resolved spontaneously after 9 weeks

Table 17.4 Pancreas injury scaling system with grading according to American Association for the Surgery of Trauma (AAST)

Grade 1	Minor hematoma without duct injury Minor laceration without duct injury
Grade 2	Major hematoma without duct injury or tissue loss Major laceration without duct injury or tissue loss
Grade 3	Distal transection or parenchymal injury with duct injury
Grade 4	Proximal transection or parenchymal injury involving ampulla
Grade 5	Massive disruption of pancreatic head

Adapted from Moore et al. [47]. With permission from Wolter Kluwers Health

(grade III–V) is suspected a magnetic resonance cholangiopancreaticography (MRCP) can be performed to fine tune the diagnosis [56]. In recent years endoscopic retrograde cholangiopancreaticography (ERCP) has evolved particularly in adult pancreatic trauma centers because it enables an endoscopic stent placement. However, a recent study in nine major pediatric trauma centers documented endoscopic stent placement in only 3 out of 131 patients with pancreatic injury [57]. This emphasizes that in most pediatric trauma centers experience with stent placements is limited with only case series reported. However, stent placement has shown its value in the adult setting and may be the best option for grade II, III or IV injuries in selected cases.

Grade I injury is predominantly treated non-operatively. The treatment of grade II and III is still being debated after more than 20 years. In the above mentioned study in nine pediatric trauma centers 20 patients with grade II and III injury were treated operatively and 45 were treated non operatively [57]. Mortality did not differ between the groups and pseudocyst formation was the major complication in both groups (Fig. 17.3b). The latter finding is in conformity with earlier studies [58]. In both studies pseudocyst formation was higher in the non-operative group. However, more than half of all pseudocysts resolve spontaneously; otherwise they can be drained percutaneously or by cystogastrostomy. Fistulas occurred more often in the operative group; these generally resolve with non-operative treatment as well. Long term outcome may be similar as well. Several studies have shown that complete transections of the pancreatic duct seem to heal without surgical treatment, probably due to recanalization occurs or atrophy of the tail of the pancreas [59, 60]. Atrophy occurs in more than 70 % of the patients and thus gives a similar long term outcome as after surgery in which the pancreatic tail is resected. Thus, either way, operative or non-operative treatment, almost always the outcome is a pancreas with loss of the pancreatic tail but normal endocrine and exocrine functioning.

Non-operative management includes nasogastric decompression and bowel rest. Nutrition is given total parenterally or enterally by a nasojejunal tube, for the duration of the bowel obstruction. Additional management includes the administration of appropriate analgesia and proton pump inhibitors or H2 antagonists. Administration of prophylactic intravenous antibiotic treatment and somatostatine or octreotide to limit exocrine function is not evidence based. Operative treatment varies from a distal pancreatectomy to duodenal diverticularization or a Roux-Y reconstruction to the stomach in case of combined duodenal and pancreatic injury [57, 61]. The latter is often done in a second stage after a damage control procedure which includes tail resection and peripancreatic drainage. This procedure was found feasible laparoscopically and spleen sparing in case of a distal pancreatectomy [62].

Hollow Viscus Injuries

Blunt hollow viscus injuries are relatively rare abdominal solid organ injuries in children. They are a diagnostic challenge in every trauma room and need early emergency repair. Despite new technologies and multidetector scanners, approximately 20 % of intestinal perforations are initially missed on CT scan [63]. The diagnosis may further be delayed by the fact that intestinal injury is part of a multi-organ trauma and not the focus of initial interest in more than 50 % of cases. Delay in diagnosis is generally considered to significantly increase morbidity after hollow viscus injury, although this was recently challenged by the APSA Committee on Trauma Blunt Intestinal Injury Study Group [64].

The mechanism of gastric and duodenal injury in children mostly differs from that in adults. In adults it is usually the result of penetrating trauma; in children, hollow viscus injury (most commonly affecting the small bowel) is most often due to blunt abdominal trauma. The stomach and duodenum are fixed close to the vertebral column. Lap belts compress both the stomach and duodenum to the vertebral column. Gastric perforations after blunt abdominal trauma occur in no more than 2 % of cases [63]. Free intra-abdominal air is found in only two thirds of cases but the clinical picture generally is consistent with an acute abdomen which necessitates immediate surgery. Duodenal injuries are also rare and estimated to occur in 0.5–3 % of cases. Both the diagnosis and treatment are challenging. The majority of duodenal injuries are hematomas, more than 90 % of which are treated non-operatively. Surgery is usually feasible in case of perforation and is associated with relatively low mortality and morbidity rates in children. As stated above, the diagnosis may be delayed 24–48 h [65]. Therefore, the surgeon should be willing to operate on clinical suspicion alone without the confirmation of a CT scan. Virtually all patients have severe abdominal pain and on physical examination signs of peritoneal irritation presenting with tenderness,

rebound pain and guarding of the abdomen. Colonic injury is less likely to occur. Its clinical picture is similar to small bowel injury, although cecal or sigmoid perforations may show retroperitoneal air leakage on CT scans. Regardless of the site of hollow viscus injury, early surgery is warranted in all cases to prevent further contamination. Resection and primary repair are safe in most pediatric cases although a colostomy should be considered in case of severe associated injuries. When there are signs of metabolic acidosis, coagulopathy and hypothermia (Fig. 17.2), it is recommended to simply close the perforated bowels with a stapler device and plan a second look after 24 or 48 h (damage control surgery).

Diaphragmatic Injury

Although technically not an intra-abdominal organ, the diaphragm is the uppermost limit of the abdominal cavity. Injury of the diaphragm, which is rare, is caused by massive compressive forces to the abdominal cavity, creating high intra-abdominal pressures with rupturing of diaphragmatic muscle. In almost 80 % of the cases multiple injuries are present. Symptoms range from none to mild dyspnea with nausea or vomiting to severe cardiorespiratory compromise. Physical clues are diminished pulmonary sounds, intrathoracic bowel sounds and a concave scaphoid shaped upper abdomen (Gibson's sign). Chest radiograph will reveal the diaphragm injury in only 25–50 % of the cases. Suggestive findings are inability to trace the left diaphragm, abnormally elevated diaphragms, air fluid level or herniated bowel or stomach above the diaphragm or a nasogastric tube within the chest (Fig. 17.4). Also, with a CT scan on can easily miss diaphragmatic injuries and these injuries are often found incidentally at exploration for other injuries. There is an equal distribution between the left and right side, although injury on the right side is more frequently missed, since the liver prevents intra thoracic migration of bowel. If there is an indication for an exploratory laparotomy for any other injury, both diaphragms should be palpated. Usually it is possible to close the defect primarily after debridement. If the defect is large, a tension free Gore-tex patch can be used, similar to the repair of congenital diaphragmatic hernias [66–71].

Abdominal Wall Injury

Abdominal wall injury is rare but a specific form of injury is seen in children. Blunt abdominal trauma may lead to a traumatic abdominal wall hernia. This can occur after a low velocity impact to the abdominal wall, e.g. a handle bar injury (Fig. 17.1b). The incoming power is not strong enough to rupture the elastic skin but is strong enough to rupture the underlying fascia and muscle of the abdominal wall. Only case reports have mentioned this type of injury and the most frequent etiology was impalement on a bicycle handlebar. Patients can present with bulging of the abdominal wall or with no symptoms at all. Traumatic abdominal wall hernias can be treated non operatively with spontaneous resolution or operatively with a (laparoscopic) surgical repair [72–76].

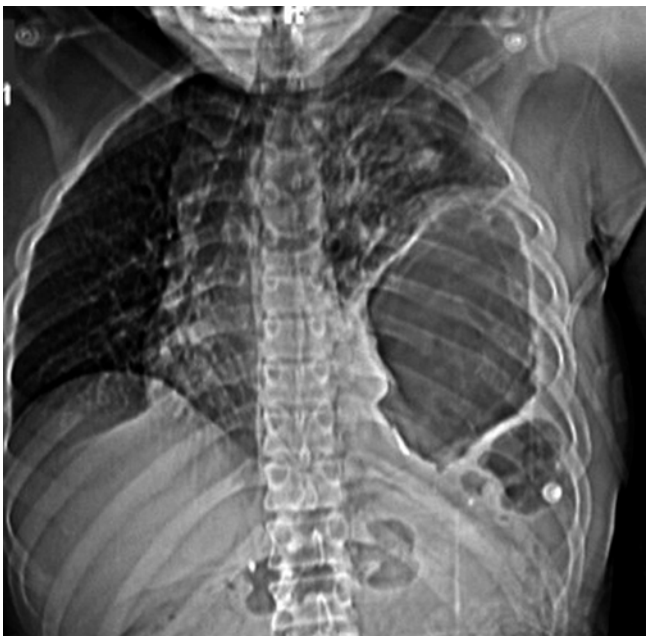

Fig. 17.4 Diaphragmatic rupture of a trauma patient with a herniated stomach above the diaphragm

Abdominal Compartment Syndrome

The abdominal compartment syndrome (ACS) is defined as a syndrome with multiple organ failure in conjunction with a high (>20 mmHg) intra-abdominal pressure [77]. The normal intra-abdominal pressure (IAP) varies due to breathing, body mass index, body positioning and contraction of abdominal musculature. In adults it normally remains between subatmospheric levels to 0 mmHg. In ACS a high IAP causes diminished perfusion of abdominal organs. Respiratory, cardiovascular, renal gastrointestinal, hepatic and central nervous systems homeostasis can all be compromised. Risk factors for ACS are multiple trauma and burns, extensive fluid resuscitation for treatment of shock, intra- and retroperitoneal bleeding, acidosis, hypothermia and coagulopathy. Serial measurement of IAP with an intravesical catheter may guide the need for (non-operative) medical or surgical strategies. In addition, findings on CT scan can be helpful. They include narrowing of vena cava, direct renal compression or displacement, thickening and enhancement of bowel walls, diminished diameter of the aorta and a relative increase in the anterior-posterior diameter compared

with the transverse diameter of the abdomen. Non-operative strategies for ACS include proper positioning of the patient (head elevation <20°), nasogastric and colonic decompression, adequate but no excessive fluid resuscitation, diuretics and continuous renal replacement therapy and percutaneous catheter decompression of free abdominal fluid. Surgical decompression of the abdominal wall is the definitive treatment for ACS but leaves patient with an "open abdomen" and greater risk of infections, fistula formation and feeding disorders. Temporary abdominal closure is obtained by several methods such as the 'Bogota bag', towel clips and vacuum assisted closure devices. Definitive closure must to be postponed until the factors that cause high IAP are resolved. ACS is rarely found in pediatric (trauma) patients. This may be due to higher elasticity of the abdominal wall, less aggressive fluid resuscitation with fluids or underrecognition of the syndrome in comparison with adults. Nonetheless, in a study with pediatric intensive care patients, a beneficial effect of decompression laparotomy was suggested to be present when IAP exceeded >12 mmHG [77, 78]. The major comment on this study is that the IAP was not very high and e.g. did not exceed abdominal pressures used at laparoscopy.

Penetrating Trauma

Only 10 % of abdominal injury in children is due to penetrating trauma. While the management of blunt trauma is guided by the stability of the patient and the associated injuries, that of penetrating trauma is completely different. Stab injuries may have predictable injury patterns since there is a straight trajectory. Gunshot injuries, however, are more unpredictable. The high energy impact produces deeper wounds and more tissue destruction. Besides, the trajectory is often not certain, which limits anatomic diagnosis. Gunshot injuries may affect the children more severely because their vital structures are concentrated within a smaller cross-sectional area; more vital organs can be injured. Hollow viscus organs, like small bowel and colon, are most frequently injured. Anterior abdominal penetrating trauma is associated with retroperitoneal organ injuries, especially in the case of gunshot injury. Most trauma centers recommend a mandatory laparotomy from subxiphoid to pubic ramus, in which the diaphragm and the retroperitoneum should be inspected, even if there is no preoperative sign of diaphragmatic or retroperitoneal injury. Therapeutic laparoscopy has been limited to penetrating trauma with simple trajectories (stab wounds) or solid-organ injuries. In recent years selective non operative management has been propagated in one third of gunshot injuries and stab wound injuries, especially if there is a tangential trajectory. The benefits of successful nonoperative management should be weighed against the risk of missed hollow viscus injuries and delayed treatment [79, 80]. Abdominal CT scan is generally made but has limited usefulness in penetrating trauma; generally it is a poor predictor of hollow viscus injury. However, it may help to determine the trajectory [79–85].

Conclusions

Abdominal trauma in children is rare and requires individualized management. Both non operative treatment and emergency surgical treatment should be adapted to the type of injury sustained. In the past two decades outcome of major abdominal trauma have improved significantly due to better diagnostic procedures, advances in surgery and critical care, and, furthermore, improved trauma care systems with referral of severely traumatized patients to Level I (pediatric) trauma care centers.

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Genitourinary Trauma

18

Shumyle Alam and Daniel Robertshaw

Abstract

Trauma is the largest single cause of death in children and adolescents in the United States. The genitourinary (GU) tract is certainly at risk for injury in the child, and blunt trauma has been the reported etiology in upwards of 90 % of all cases of pediatric GU trauma. The relative lack of protection of the GU organs makes them more susceptible to injury.

Advancements in imaging, surgical and medical management, and ICU care have improved outcomes and decreased morbidity. We have better treatment algorithms based on large case series, and are slowly starting to standardize approached to pediatric GU trauma management. Although long term data is lacking regarding long term follow-up and acquired morbidity, efforts are being made at major trauma centers to more appropriately track outcomes.

The following chapter will serve as a summary of GU trauma in children as well as a review of literature to date regarding the diagnosis, treatment, and follow-up of urinary tract injuries. We hope that the chapter will inspire individuals to more accurately standardize approaches, track outcomes, and further validate current treatment guidelines. The creation of registries and a standard regarding long term follow-up of children with these injuries will add to the literature and perhaps bring us closer to understanding of who is at risk from long term sequelae of their injuries.

Keywords

Pediatric genitourinary trauma • Renal laceration • Congenital urinary tract malformation • Blunt trauma

Introduction

Trauma is the largest single cause of death in children and adolescents in the United States. The genitourinary (GU) tract is certainly at risk for injury in the child, and blunt trauma has been the reported etiology in upwards of 90 % of all cases of pediatric GU trauma. The kidney is involved in 10–20 % of all blunt traumatic injuries and is the most frequently injured organ of the genitourinary system [1]. Depending on the mechanism of the trauma, there is a greater than 90 % reported incidence of concomitant organ injury, including both bony and visceral structures of the chest, abdomen, and pelvis. Overall mortality in children is more likely from multi-organ trauma than from isolated renal injury.

The most common causes of severe pediatric trauma are motor vehicle accidents, pedestrian struck by vehicle, and cyclist struck by vehicle [2]. Bicycle injuries, penetrating trauma, sports, sexual abuse, and non-accidental trauma

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are other important sources for genitourinary tract injury. Bicycle injuries are the most common sporting activity related cause of renal injury in children and are associated with higher grades of renal injury [3]. Unfortunately, penetrating injuries are becoming more frequent in the pediatric population as well. However, isolated genitourinary injury is rare with penetrating trauma and overall surgical exploration rates are higher [4]. The kidney is involved more commonly with gunshot wounds than stab wounds and is associated with a higher grade of injury than blunt trauma [5].

Since most patients with genitourinary trauma will have concomitant injuries, initial observation in the PICU is a frequent occurrence. Unfortunately, the initial impression in the PICU is an overall poor predictor of survival or morbidity. It is only with time and observations that these predictions can be accurately made [6]. A deeper clinical understanding of genitourinary trauma may serve in part to better tailor protocols and utilize PICU time more efficiently.

The long-term morbidity from isolated genitourinary trauma, especially the delayed consequence of renal injury is poorly understood. Outcomes regarding urethral injury and impotence are beginning to be reported. Long term consequences from renal injury are surprisingly absent in the literature. The following chapter focuses on the assessment, mechanism of injury and management of genitourinary trauma in the pediatric setting.

Incidence

As stated above, the kidney is the most commonly injured GU organ, with involvement in over 60 % of GU injuries [7]. Approximately 90 % of renal injuries in children are attributed to blunt force trauma. When associated with penetrating trauma, however, the severity of the renal injury is increased. Overall, genitourinary organs are injured in less than 3 % of all pediatric traumas [2]. Importantly, when GU organs are injured there is concomitant visceral or bony injury in upwards of 80 % of cases. Therefore, the presence of GU trauma should raise the clinical suspicion for other severe injuries.

Children have unique anatomic differences that place them at increased risk for genitourinary trauma compared to adults. The pediatric kidney is at greater risk for injury since it is located lower in the abdomen and is not protected by the rib cage and the cupola of the diaphragm. There is also a lack of protective tissue and fat around the kidney. This lack of tissue, known as Gerota's fascia, puts the child at increased risk for renal laceration, expanding hematoma, and extravasation of urine. The mobility of the kidney places the renal pedicle at risk with deceleration injuries. Additionally, the pediatric rib cage is more pliable, and the abdominal musculature less well developed compared to that of the adult [8]. Children are therefore at a greater risk of internal injury with blunt trauma.

Blunt trauma resulting in renal contusion is the most commonly seen injury. The renal pedicle is also at risk, as shearing forces can injure the artery or the vein. The artery is more predisposed to laceration which can lead to dissection and thrombosis. This is due to the relative mobility of the pediatric kidney. Flexion/extension injuries seen in motor vehicle crashes with lap belts are an important cause of renal pedicle injuries [7]. Associated GU abnormalities, whether congenital (e.g., ureteropelvic junction obstruction, horseshoe or ectopic kidney) or acquired (e.g., Wilms' tumor) increase the susceptibility to injury. For example, the abnormalities associated with hydronephrosis put the kidney at risk of more severe injury even in the setting of minor trauma, causing a disproportionate degree of hematuria relative to the severity of the traumatic injury [9]. One must be aware of the potential for pre-existing congenital renal abnormalities when performing a CT scan to evaluate the trauma [9, 10].

Clinical Presentation

The evaluation of the genitourinary tract is part of the overall assessment of the patient after a traumatic injury. Initial evaluation takes place in the trauma bay, but missed or late consequences of genitourinary injury will be picked up in the PICU. The mechanism of injury is a critical piece of information, as it has a prognostic and predictive value regarding the involvement of the genitourinary tract. Physical findings such as flank or abdominal ecchymosis can alert the clinician for underlying renal injury, though 25 % of patients with isolated renal injury will have unremarkable exams [11]. There is a high incidence of concomitant visceral and bony injury in pediatric trauma, causing increased overall mortality. Aggressive evaluation and diagnosis of multi-organ injury is critical. The classic presentation of renal injury is flank pain and hematuria (microscopic or gross). Other symptoms such as abdominal tenderness, flank mass, flank hematoma, perineal trauma with hematoma, and fractured ribs are also important signs of potential renal trauma.

Gross hematuria suggests an injury to the genitourinary tract, but should not be the only cause for concern. As previously stated, those patients with hematuria disproportionate to the mechanism of injury may have a pre-existing renal abnormality. Moreover, the degree of hematuria does not necessarily correlate with the severity of the injury, and children with renal pedicle injuries and/or pedicle disruptions may even present without hematuria. There is some evidence that up to 70 % of grade 2 or higher renal injuries will lack either gross or microscopic hematuria [10].

Examination of the lower abdomen and pelvis is critical for the assessment of genitourinary trauma. Scrotal or perineal ecchymosis, blood from the urinary meatus, lacerations, and swelling are all highly suggestive of genitourinary

involvement. A boggy mass or upward displacement of the prostate on digital rectal exam suggests urethral injury in the adolescent male or adult but is a poor test in the child [12]. Digital rectal exam does not appear to be a sensitive test in children for documenting the involvement of the lower urinary tract after pelvic trauma [13].

Pelvic fractures may be associated with lower urinary tract and rectal involvement. Certain fractures are at greater risk than others. Associated bladder injury is seen with widening of the symphasis pubis or sacroiliac joint and fractures of the sacrum. Widening of the symphasis is most often seen with associated rectal injuries, bladder injury, and urethral injury [14]. These types of pelvic fracture associated with any degree of hematuria should alert the clinician that there is an associated urologic injury. Fractures of the lower ribs should alert one to the possibility of concomitant renal injury.

Diagnosis

Hematuria

Gross hematuria is without question a sign that warrants further evaluation, but there is controversy regarding the interpretation and predictive value of microscopic hematuria [15]. Significant hematuria is defined as greater than 50 red blood cells (RBCs) per high powered microscopic field (HPF). In contrast to the adult population, hematuria without shock may be indicative of a severe injury in the pediatric population. In most centers the urinalysis is obtained after catheter placement, so consideration must be given to the presence of an underlying urethral injury before a catheter is inserted. Failure to do this can result in making a urethral injury worse and causing more morbidity. Blind catheter placement when there is any concern for a urethral injury is to be avoided.

Radiographic Imaging

The decision for imaging in children should be based on the clinical picture, the mechanism of the trauma, and the index of suspicion for an injury. Application of the adult criteria for imaging (gross hematuria, or microscopic hematuria >50 RBC's per HPF with shock, significant organ injury, deceleration injury and penetrating trauma) to the pediatric patient is not indicated. The major drawback in children is the fact that they do not routinely become hypotensive and that shock is not necessarily the best marker of the severity of renal injury [16]. A review by Thorp et al. in 2010 found that the microscopic urinalysis has only moderate discriminate power for the prediction of urinary tract injury. CT scan was considered the standard for diagnosis of injury in their study population and they found that injuries were found even in the absence of hematuria. Their study suggests that the urinalysis alone is not a good indicator for the need for radiographic imaging in trauma [15].

Radiologic evaluation is generally recommended after any penetrating trauma where urologic injury is suspected, any significant acceleration/deceleration (i.e. motor-vehicle collisions, falls from over 15 ft, or blunt trauma from a projectile), trauma resulting in physical signs of injury including flank ecchymosis, peritonitis, or bony injury (rib cage, thoracic and lumbar spine, pelvis, or femur), any gross hematuria, and microscopic hematuria with shock [7, 17, 18]. Microscopic hematuria alone is not an indication for imaging [19], as the positive predictive value for detection of renal or GU tract injury with microscopic hematuria alone is very low. For example, a meta-analysis of the relevant publications reveals that of 2,032 cases of microscopic hematuria following blunt trauma, only one patient had a clinically significant injury [20]. Gross hematuria in the presence of pelvic fracture mandates cystography, though urethral catheter placement may need to be performed under fluoroscopic guidance after determining that the urethra is not injured. In the cases of urethral disruption, a suprapubic tube should be placed. In the child this is ideally placed in the operating room. Radiologic guidance and confirmation of placement is recommended if percutaneous access is employed. In the setting of a pelvic fracture, the hematoma can sufficiently displace the bladder superiorly which could complicate placement of a percutaneous suprapubic tube.

The most sensitive and specific test to evaluate renal trauma is computed tomography (CT) with intravenous contrast. This should be obtained in three phases, including a precontrast phase, immediately post-contrast phase, and a delayed phase (15 min). As detailed this will help identify renal masses, renal injury, and collecting system injuries, respectively (Figs. 18.1, 18.2, 18.3, and 18.4). The total radiation dosage with a three phase CT scan for a child is quite high, ranging from 12 to 20 mSv. In order to limit radiation exposure careful consideration should be employed before proceeding to the 3rd scan, especially if renal injury is not likely to be associated with delayed urinary extravasation. The pediatric patient has a higher risk from radiation exposure than the adult. Specific trauma protocols should be adjusted as clinically needed regarding scanning and repeat CT studies. The total radiation dose may be reduced if the studies are appropriately protocoled and one does not necessarily have to reduce the number of scans [21]. This is clinically relevant as the child has a longer time frame for the development for radiation induced cancer [22].

If the patient's stability is of concern imaging options include a single post IV contrast phase CT or a "one shot" intravenous pyelogram (IVP). A single phase CT will be more likely to miss isolated ureteral injuries. The IVP is

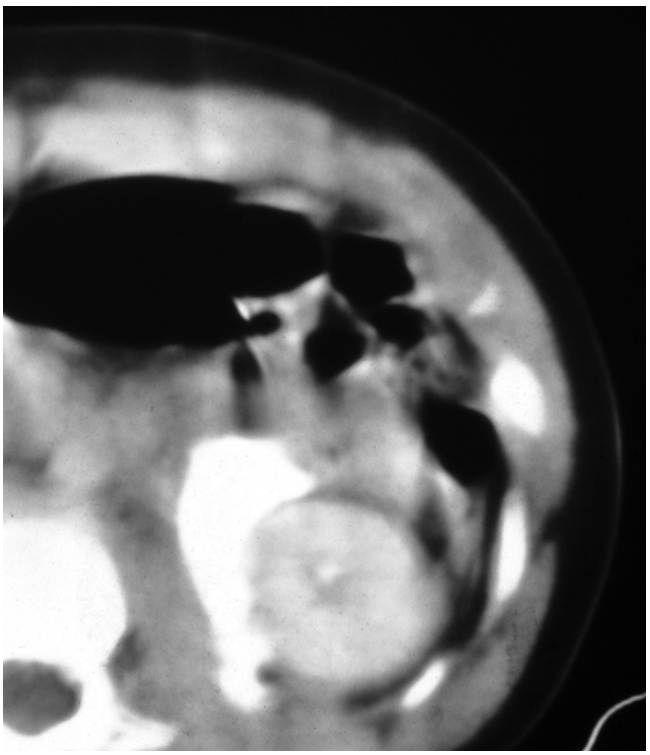

Fig. 18.1 A 7-year old male involved in a motor vehicle accident associated with rapid deceleration causing a left ureteropelvic junction (UPJ) disruption. Note extravasation of contrast at the level of the left UPJ. Images more distally did not demonstrate a ureter

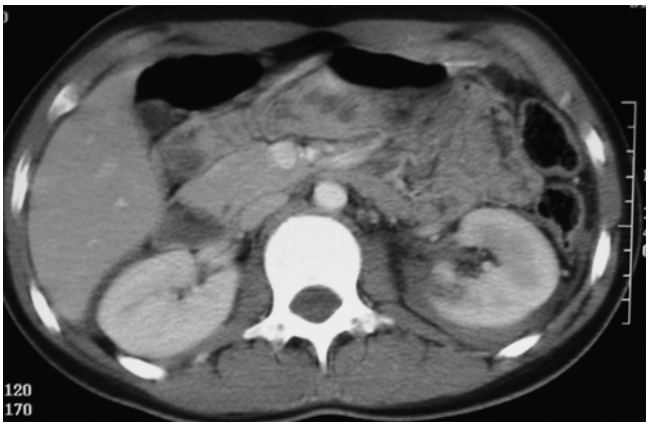

Fig. 18.2 A 12-year old female with left flank pain after fall from horse. CT demonstrates a Grade III left renal laceration with small perinephric hematoma

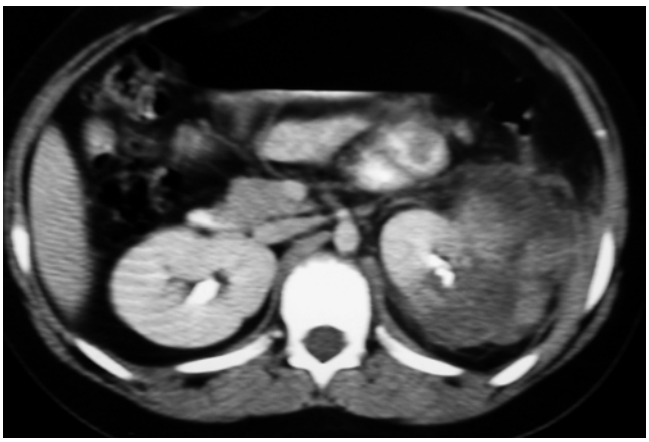

Fig. 18.3 Excretory phase on CT of a 13-year old male involved in an ATV rollover accident with left flank pain and gross hematuria. A grade III renal injury without contrast extravasation is present

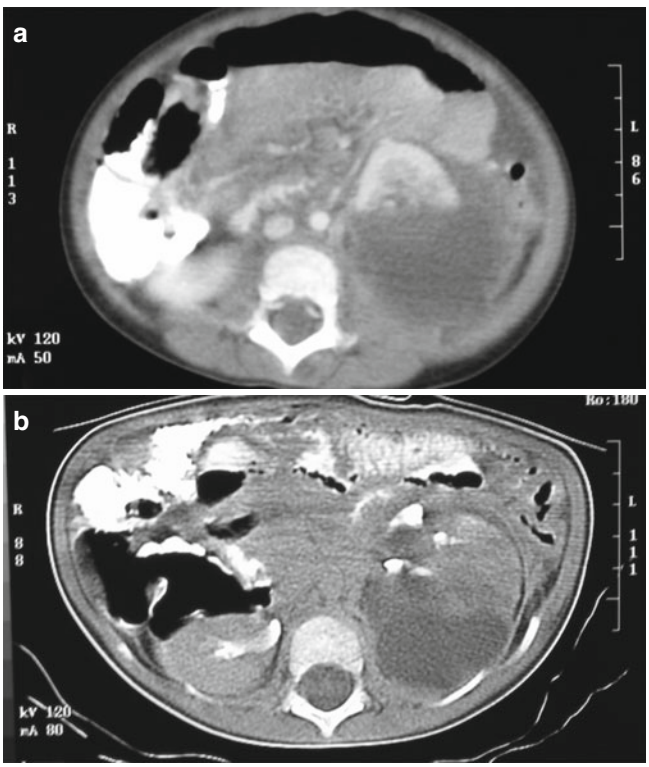

Fig. 18.4 (**a**) A 2-year old female with a Grade IV left renal injury after suspected child abuse. A large left perinephric hematoma has developed with apparent non-perfusion and disruption of the posterior kidney. (**b**) Delayed images demonstrate contrast extravasation. This child required operative intervention with left heminephrectomy

performed by administration of a 2 mL/kg bolus of radiographic contrast and obtaining a single supine radiograph of the abdomen 10 min later. This abbreviated study is sufficient to provide information regarding the kidney suspected of injury and most importantly will evaluate contralateral renal function when a nephrectomy is considered. Hydration and resuscitation status is critical for this test. In the setting of hypotension or poor resuscitation, the sensitivity of this study is reduced [23]. A further important limitation is that the IVP cannot stage renal injuries.

The Focused Assessment with Sonography for Trauma (FAST) scan with serial physical exams provides an additional imaging option. There is evidence that a negative

Table 18.1 Imaging guidelines

1. Significant mechanism of injury (deceleration or high-velocity blunt injury)
2. Significant physical findings (fractured ribs, spine, pelvis, or femur, flank ecchymosis, or peritonitis),
3. Gross hematuria
4. Microscopic hematuria associated with shock hypotension
5. Penetrating trauma

FAST scan combined with normal serial physical exams may avoid the need for a CT scan [16]. The main utility of the FAST scan is to detect the presence of peritoneal fluid which is a relatively non-specific finding. The presence or absence of significant renal trauma may be seen with FAST, though in some older children, the kidneys may not be seen well with the abdominal probe, limiting the efficacy of the imaging modality. If a bladder perforation is suspected, this may have a role in guiding the appropriate imaging. At this point FAST cannot accurately replace CT for diagnosis of GU injuries related to trauma (Table 18.1).

Ultrasonography has the potential benefit for the follow-up of injuries, particularly renal injuries. Ultrasound is useful for detecting and following a fluid collection or suggestions of urinary extravasation. It could also aid in the detection of any post-trauma complications such as abscess formation, pseudoaneurysm, or hematoma. Eliminating or decreasing follow-up CT scans and replacing with ultrasound in this setting would reduce radiation exposures [24–26]. This is most pertinent in the PICU setting as the need for reimaging is often made when clinical signs change. A properly performed bedside ultrasound in the PICU may reduce the number of CT scans and decrease the need for transport of the critically ill patient.

Depending on the degree of concern regarding a urinary leak, a retrograde pyelogram may be performed (Fig. 18.5). The benefits of the study would be to accurately define the type of bladder, ureteral, or renal pelvis injury and allow for the placement of a ureteral stent if indicated. The significant downside of utilizing the retrograde pyelogram as part of the work-up for ureteral injury is that it requires a general anesthetic and may not allow for placement of a nephrostomy tube in the same setting, depending on the operative set-up. We tend to utilize a retrograde pyelogram in situations where the index of suspicion for injury is very high in order to avoid an unnecessary anesthetic. A missed ureteral injury is associated with increased morbidity. In children with a high index of suspicion close follow-up and repeat imaging such as ultrasound can assure that the decision for retrograde pyelography can be made safely on a case by case basis [27, 28].

The diagnosis of a urethral injury is difficult in children from clinical findings alone. When the index of suspicion is high, as in the setting of blood at the urethral meatus associated with pelvic fracture, a retrograde urethrogram is indicated. An appropriately sized Foley catheter is inserted into the urethra and the balloon inflated with 1–2 mL in the fossa navicularis of the distal urethra. Care should be taken to slowly fill the balloon and not allow the catheter to slip out of the meatus with inflation. The patient should be placed obliquely at a 45° angle under the fluoroscopic arm before contrast is injected. Failure to adhere to proper technique with this study can lead to an incorrect diagnosis (Fig. 18.6) [29].

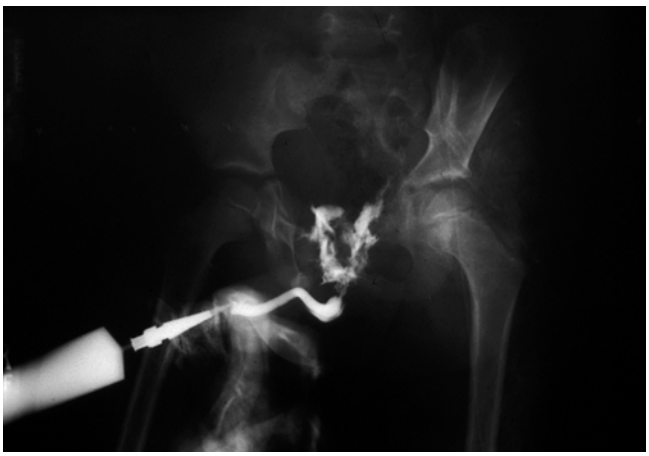

Fig. 18.5 Retrograde urethrogram after a straddle injury in a young male demonstrates complete anterior and posterior urethral disruption at the level of the urogenital diaphragm consistent with a Type III urethral injury

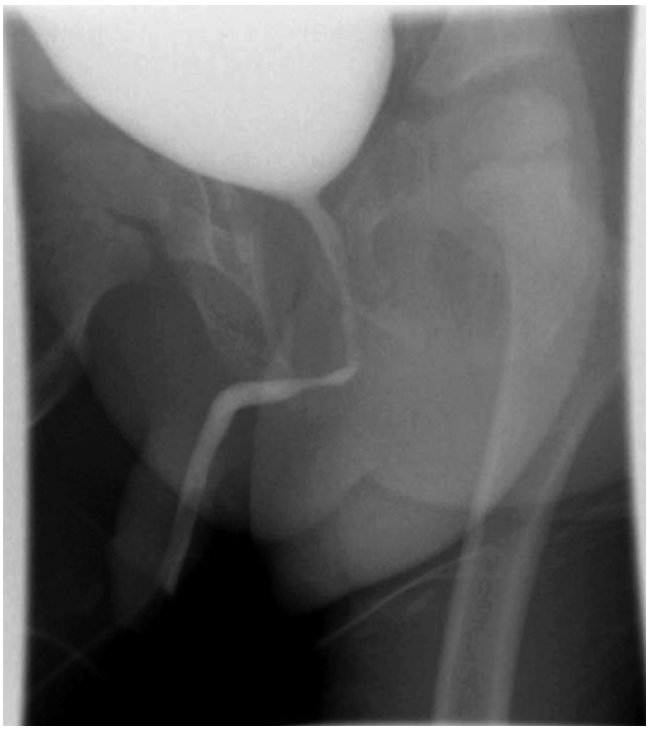

Fig. 18.6 An example of a properly performed Retrograde Urethrogram (RUG). Note the pelvis is angled allowing visualization of the posterior urethra in this normal study

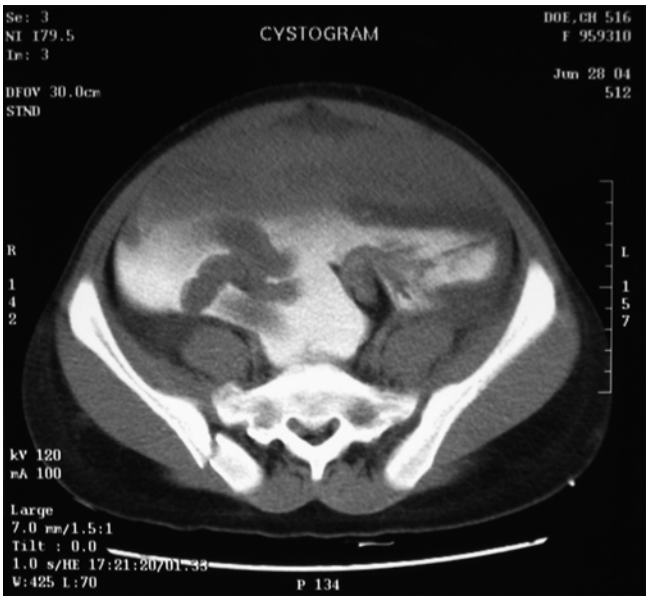

Fig. 18.7 A 12-year old female involved in a high speed motor vehicle accident. CT cystogram demonstrates an intraperitoneal bladder rupture with contrast outlining loops of small bowel

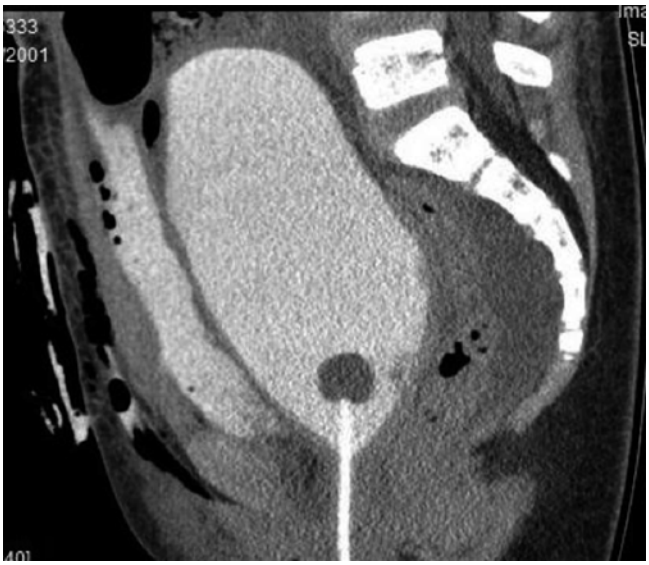

Fig. 18.8 An example of an extraperitoneal bladder injury. The bladder was filled to capacity PRIOR to the contrast CT to allow accurate imaging for an injury

When a bladder injury is suspected a cystogram may be utilized for diagnosis. Since the chance for associated injury is high in this setting, many centers utilize a CT cystogram (Fig. 18.7). The positive predictive and negative predictive value of the properly performed CT cystogram is 100 %. The sensitivity and specificity is equivalent to fluoroscopic cystogram [30, 31]. It is imperative that the test be performed correctly with the correct amount of contrast instilled into the bladder before scanning. The correct volume should be the expected bladder capacity for the child. This is discussed in detail later in the chapter. It is not adequate to simply clamp the Foley catheter and relay on post contrast images for bladder filling (Fig. 18.8).

The classification of renal injury is based on CT scan findings: Grade 1- Minimal injury with an intact renal capsule; renal contusion of subcapsular hematoma, Grade 2- Disruption of the capsule but no injury to the collecting system; perirenal hematoma, renal laceration <1 cm, Grade 3- Involvement of the parenchyma and collecting system; renal laceration >1 cm, Grade 4- Injury extending through the cortex, medulla, and collecting system with urinary extravasation; or contained hemorrhage vascular pedicle injury, Grade 5- Shattered kidney with multiple devascularized fragments; or traumatic disruption of the vascular pedicle (Fig. 18.9). This classification was created by the American Association for the Surgery of Trauma (AAST) Organ Injury Scaling Committee, which was first published in 1989. The purpose was to standardize the classification of renal injuries and was not intended to provide prognostic value. The ability of the grading system to predict prognosis came after the grading of injuries was standardized. There continue to be suggestions for modifications and there is some concern about the applicability to children especially when considering the long term morbidities from higher grade renal injuries.

Management of Renal Injury

The decision for operative versus non-operative management in this population can only be made after assessing the hemodynamic stability of the patient, the accuracy of radiographic staging, and the presence of concomitant visceral injuries. Surgical options include exploration with nephrectomy, renorrhaphy, or angiographic embolization. Absolute indications for exploration include a pulsatile retroperitoneal mass, an unstable patient as a result of renal bleeding, or failure to control initial or delayed renal bleeding by less invasive maneuvers [17]. Relative indications include patients with no preoperative imaging who are found to have a retroperitoneal hematoma and hemodynamic instability, or if the patient has a known grade 3 or higher injury and will be undergoing exploration for concomitant injuries [32]. The non-operative management of blunt renal trauma is as successful as non-operative management of injuries to other solid organs, such as the liver and spleen. In children conservative management has been met with a high degree of success [27]. The caveat to be remembered is that an adjunctive procedure may have to be performed at a later date [33]. For Grade III renal lacerations and higher, if there is no other indication for operation, the patient should be admitted, placed on bed rest with

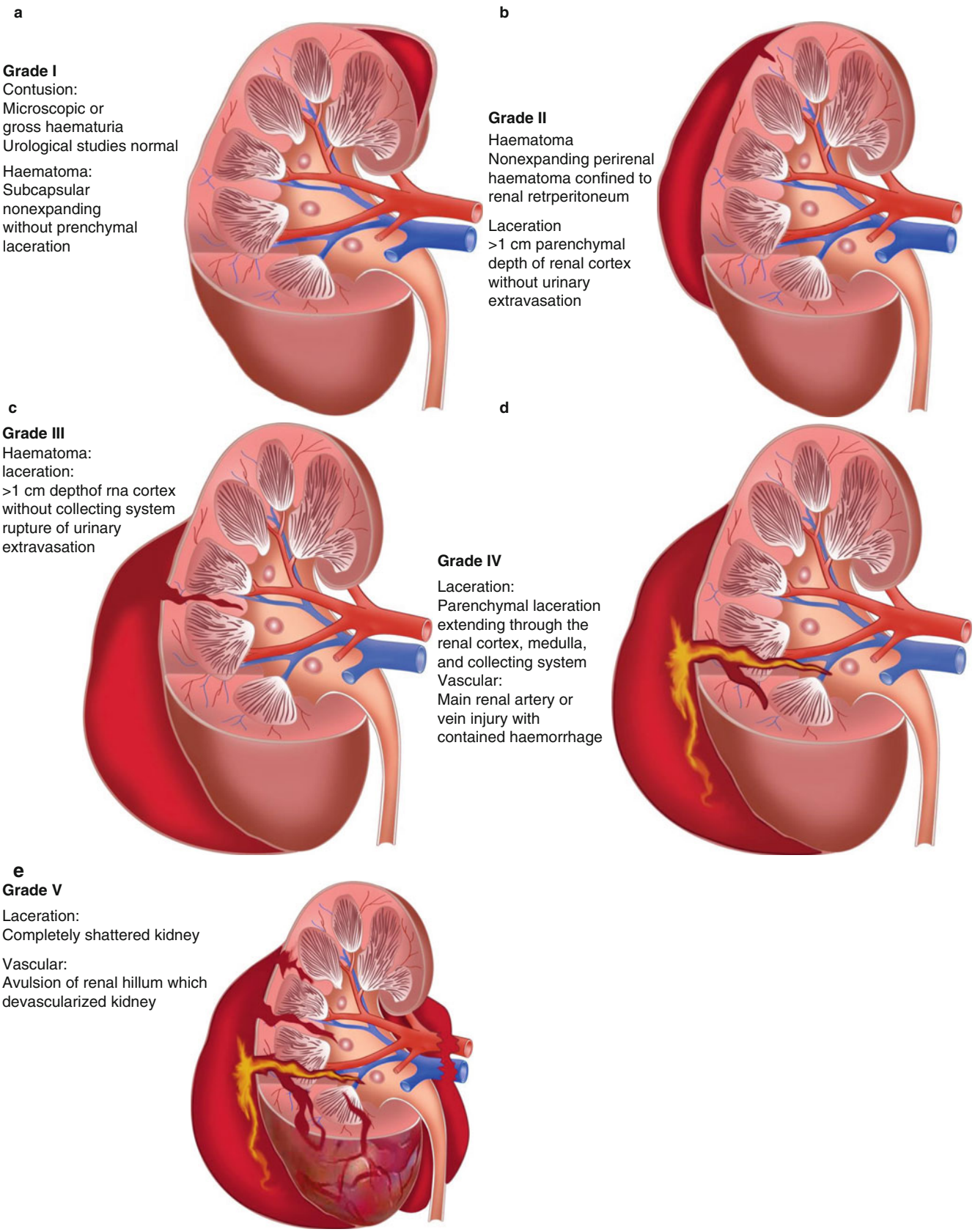

Fig. 18.9 Classification of renal injuries. (**a**) Grade I, (**b**) Grade II, (**c**) Grade III, (**d**) Grade IV, (**e**) Grade V

close monitoring (often in the PICU setting initially) and followed closely with serial hemoglobin/hematocrit levels and resolution of hematuria, if present. Serial abdominal CT scans or ultrasounds are helpful in initially evaluating stability of the hematoma and detection and of a fluid collection or urinoma. In children, repeat ultrasound is advised. In addition to decreasing radiation exposure, the procedure can be performed at the bedside in the PICU to avoid patient movement.

The protocol for checking serial labs will also vary among institutions. In general a falling hematocrit and need for repeat transfusion is a predictor of the failure of non-operative management [34]. Activity limitations after trauma are poorly understood with many centers using guidelines based on physician preference [35]. Attempts have been made to validate guidelines for bedrest in the inpatient setting for liver and splenic injury, as well as sports restrictions for this group 6 weeks after the trauma [36].

The majority of blunt renal injury in children is considered low grade (i.e., grades I–III). This is seen in 85 % of renal trauma. The remaining 15 % of trauma is grade IV and V, with grade V having the lowest incidence [2]. In patients with devascularized fragments and any grade IV, or grade V injury repeat imaging should be performed 2–3 days after injury to evaluate stability of trauma [37]. Certainly earlier imaging is warranted if the patients clinical picture changes [32]. On occasion conservative initial management of renal injuries may ultimately require operative intervention consisting of drainage, repair or nephrectomy [38]. However, as mentioned previously above, a review of the literature by Santucci et al. increasingly supports non-operative observation of blunt renal trauma [39].

Clinical exam and index of suspicion will factor prominently with management of renal injury. Imaging is not a surrogate for physical exam and judgment. Grade IV and V renal injuries are associated with increased risk of delayed complications [33]. These complications include bleeding, urinary extravasation, abscess, and aneurysm. To blindly protocol repeat imaging for all grades of renal injury will likely result in increased costs without value. We would suggest allowing the clinical picture to dictate imaging in the acute setting for Grade I–III renal injury but would recommend follow-up imaging on all Grade IV and V injuries [37].

Complications

Short term complications of non-operative management of renal trauma are secondary to bleeding, abscess formation, and urinomas. These complications are generally seen after injuries in which segments of parenchyma are devascularized or extensive hemorrhage and urinary extravasation have occurred. This is also seen in the setting of pre-existing congenital renal anomalies such as ureteropelvic junction obstruction. A high index if suspicion is necessary, and imaging should be obtained in the setting of penetrating renal injury [37].

Long-term complications are formation of arteriovenous fistulae, encysted hematomas, and development of hypertension. Long-term management of post-renal injury patients should include observation for the development of hypertension. There does appear to be a decrease in renal function that is directly correlated with the grade of renal injury [40]. A possible etiology for the development of hypertension is activation of the Renin-Angiotensin-Aldosterone System (RAAS). This can be related to parenchymal compression due to hematoma, arteriovenous fistula, and segmental scar formation. Long term follow-up studies after renal trauma are rare but there does appear to be some risk of development of hypertension after trauma [41]. Monitoring for hypertension in the acute and chronic setting is warranted [42]. The best way to screen patients is not clearly understood. Yearly or biannual measurement of blood pressure is suggested as well as urinalysis to screen for proteinuria. Imaging such as ultrasound can be helpful if hypertension develops to screen from a vascular or parenchymal cause. A baseline nuclear scan may be helpful such as a Dimercaptosuccinic acid (DMSA) scan [41, 43, 44]. A baseline measurement of GFR is also helpful because there is data to suggest that Chronic Kidney Disease (CKD), once present can be progressive and is related to a risk of development of hypertension [45]. The progression of CKD once present is independent of the initial grade of renal injury, but the risk of CKD increases with higher grade renal injury. Our understanding of the development of hypertension is changing and conventional measurement in the office with an automated cuff may miss some cases of early hypertension [46]. Imaging may be most helpful as well as obtaining a measurement of GFR. This will allow the designation of a CKD stage which can help guide management [47].

Historically, most pediatric surgeons and urologists have cautioned against contact sports such as football, lacrosse and hockey in patients with a solitary functional kidney or patients that have sustained a renal injury [48]. Analyses of the risk of sports and renal injury have demonstrated that this advice is not warranted [49]. Though contact sports seem as if they would be the highest risk activity for renal injury, bicycle crashes were shown to have a fivefold increase in incidence of renal injury compared to sports in a review by McAleer and colleagues [50, 51]. When counseling parents and children the published data should be addressed and the decision to restrict sports indefinitely should be tempered [52].

The incidence of penetrating injury is unfortunately increasing in pediatric centers [4]. Management often involves surgical exploration due to the increased chance of

associated organ injuries. There are cases and reports of conservative management of penetrating renal trauma in select cases. Like the conservative management of blunt renal injury, non-operative management of select penetrating renal trauma has been associated with decreased morbidity [53]. The selection criteria for non-operative management include an absence of concomitant injury, hemodynamic stability, and a patient that can be clinically evaluated. The grading of the renal injury remains the same and is staged by CT scan. One also must have a high index of suspicion for a potential urinary leak and repeat imaging is especially warranted.

A vascular injury to the kidney may occur in the setting of penetrating trauma. The child is susceptible to this type of injury do the relative mobility of the kidney in the abdomen. The kidney is therefore at risk during sudden deceleration injuries. The left side is slightly more at risk due to the relative length of the renal artery as compared to the right side [54]. These patients tend to be more severely injured, have an increase need for transfusion, and frequently (almost always) have other associated major injuries [54]. The outcomes for these injuries are poor with regard to renal salvage. Non-operative management is usually successful with operative management usually resulting in nephrectomy [55]. ICU monitoring for these patients is imperative as these patients will in general be much sicker than those with renal parenchymal injury. Attempts at revascularization surgery should be limited to bilateral disease or a solitary kidney as the surgical outcomes are poor [56]. The optimal treatment for this type of GU trauma has not been established.

Specific Types of GU Trauma

Ureteral Trauma

The ureters are well protected by the spine, paravertebral muscles, and viscera. The pelvic ureters have additional protection from the bony pelvis. With this amount of protection there is usually a considerable amount of force needed to cause ureteral injury, therefore ureteral and ureteropelvic junction (UPJ) injury is rare. The mechanism of injury is typically extreme flexion of the trunk causing avulsion force or partial ureteral tear. Forces interact on the more mobile kidney compared to the relatively immobile ureter [9, 57]. Injuries may also occur as a result of severe extension of the torso, rapid deceleration, and blunt or penetrating trauma. If a ureteral injury is identified there is a 10 % incidence of concomitant renal or bladder injury and 90 % chance of concomitant abdominal organ injury. As such these patients tend to have multiple injuries and a mortality rate >30 % [5, 58].

With the advent of increasingly minimally invasive surgical techniques there has been an increase in iatrogenic ureteral injury. These injuries are typically seen in the mid ureter. Penetrating trauma, especially gun violence, can also be associated with ureteral damage. High velocity rounds can have a widespread thermal effect, even if the path of the bullet does not directly involve the ureter. This can lead to a delayed urine leak typically 4–5 days after injury in response to necrosis. Delay in diagnosis is unfortunately common, with only 40–88 % of ureteral injuries being discovered in the first 24 h [2].

Diagnosis

Because of the rarity of injury to this structure a high index of suspicion is requisite. Hematuria is rarely seen with ureteral injury, with it lacking in up to two-thirds of patients [57]. These injuries are best evaluated by an abdominal CT scan with intravenous contrast; of specific interest is the excretory or delayed post-contrast phase. Findings suggestive of ureteral injury may include contrast extravasation (specifically medial to the renal pelvis in the case of UPJ disruption), perinephric fluid collection, absence of contrast in the ureter, and dilation of the ureter. Additional imaging modalities include anterograde urography via a percutaneously obtained renal access or retrograde urography during cystoscopy. Retrograde ureteropyelography performed with concomitant cystoscopy and fluoroscopic imaging is a reliable study for the diagnosis of injury versus ureteral integrity, however its utility in the acute trauma setting is usually limited until other injuries are controlled and the patient is stable. Intra-operative assessment can be made with direct injection of methylene blue into the renal pelvis to identify the level of injury [59].

Management

Surgical options include endoscopic management with placement of intraluminal ureteral stents, primary anastomosis with or without mobilization of the kidney or bladder, creation of a bladder flap (psoas hitch), renal autotransplantation, ureteral substitution (i.e. ileal ureter), or nephrectomy. Traumatic avulsions are best repaired immediately. Some advocate for immediate repair if the injury is identified within 5 days of trauma, with delayed repair (>12 weeks) for those injuries discovered after 6 days. A careful literature review suggests that the studies recommending early or delayed surgical intervention are likely underpowered to make a generalized conclusion regarding optimal time for successful treatment [60]. Partial tears are usually repaired but they can be managed non-operatively at times. Choice of surgical repair typically depends on the level of injury, patient stability, timing of recognition of injury, and severity of injury. If delayed repair is pursued then urinary diversion can be undertaken via percutaneously placed nephrostomy tube, or trans-cutaneous ureterostomy.

Bladder Trauma

Injury to the pediatric bladder is rare, attributable to its location within a pliable bony pelvis and relative elasticity compared to the adult bladder. However in infants and toddlers, or when distended with urine it does become an abdominal organ. Under these conditions it is less well protected. Overall bladder injury accounts for 2 % of abdominal injuries requiring surgery. In patients with pelvic fractures there is a 0.5–3.7 % incidence of concomitant bladder injury [61]. Mortality rates approach 20 % when bladder injuries are identified [62]. The most likely causes of injury include blunt trauma, traumatic umbilical artery catheterization, traumatic urethral catheterization with perforation, and posterior urethral valves.

Patients with bladder trauma usually present with diffuse lower abdominal pain and tenderness and may also have hematuria. Injuries are defined as either extraperitoneal or intraperitoneal, which often coexist in the same patient. Intraperitoneal injury is usually the result of forces on a full bladder causing rupture at the bladder dome and urinary ascites. These patients may have signs suggestive of chemical peritonitis from the extravasated urine including physical exam findings, azotemia, acidosis, and ileus. Extraperitoneal injury is typically a result of shearing forces applied to the fixative points of the bladder at the bladder neck and vagina. Pelvic fractures are seen with the latter.

Diagnosis

Absolute indications for further evaluation include any penetrating trauma, blunt trauma with gross hematuria and a pelvic fracture, or blunt trauma with inability to void [63]. Bladder injuries are diagnosed by cystography. If blood is noted at the urinary meatus, urethral injury must be ruled out with a retrograde urethrogram (RUG) before inserting a catheter. An appropriate cystogram for trauma requires that images be obtained with the bladder filled to capacity as well as post drainage images to look for extravasated contrast. Films must be taken in the anteroposterior, lateral, and both oblique alignments. Extraperitoneal injury has a characteristic flare appearance from contrast tracking along tissue planes, while intraperitoneal injury reveals contrast outlining loops of bowel. The bladder capacity for the infant to the 2 year old is calculated as 7 mL/kg. For the child above 2 years of age the formula is (Age in years + 2) × 30 = capacity in mL [64, 65]. A single scan is sufficient but will require the images to be reformatted in order to accurately identify the images. If the study is not diagnostic, consideration should be given to performing a fluoroscopic cystogram. The CT cystogram is also a valuable study to assess the patient who has undergone a bladder augmentation in the past in whom bladder injury is suspected. This unique group of patients may present with abdominal pain after traumatic injury but may also present after failure to catheterize for a long period of time. The adolescent who has failed to catheterize after a period of alcohol consumption is at increased risk [66].

Management

Extraperitoneal bladder rupture is managed by an indwelling catheter for 10–14 days with repeat cystography at that time. Intraperitoneal bladder rupture requires repair. Intraperitoneal urine is rapidly absorbed leading to azotemia and acidosis. Surgical repair is also recommended for penetrating trauma, bladder neck lacerations, identification of a bony spicule protruding into the bladder, concomitant vaginal laceration, or concomitant rectal laceration. After primary repair catheter drainage is essential, and is left in place for 7–10 days. Once again cystography is repeated prior to catheter removal. Failure to recognize a bladder neck laceration can result in persistent urinary extravasation which increases the risk of infectious sequelae including urinoma, abscess, osteomyelitis, urinary incontinence. The competence of the bladder neck can be ascertained with radiographic studies.

Urethral Trauma

Urethral injuries are classified based upon whether they involve the posterior or the anterior urethra. The posterior urethra extends from the bladder neck to the bulbous urethra and includes the prostatic urethra. Injuries to this area are generally the result of severe blunt trauma including motor-vehicle trauma. In patients with pelvic fractures, 5 % have associated posterior urethral injuries. Ten to thirty percent of these patients also have bladder ruptures [61]. Pediatric pelvic fractures are more unstable, which lends to a severe displacement of the prostatic urethra with an increased risk of complete posterior urethral disruption. There is also increased complexity when bladder neck, sphincter, and urethral lacerations coexist. Future sequela includes erectile dysfunction and urinary incontinence. It appears that the severity of the injury and not the initial treatment modality cause these complications [67, 68].

Anterior urethra and bulbar urethral injuries are usually caused by straddle trauma, urethral instrumentation or circumcision. Most often there are associated genital injuries including penile hair tourniquet and injuries related to the infant circumcision. In girls, pelvic fractures are four times more likely to result in urethral injury as compared to adult women [69, 70]. There are concurrent vaginal and rectal lacerations in 75 and 30 % of female urethral injuries, respectively.

Diagnosis and Management

Classically these children are unable to void and are often seen with a distended bladder, associated genital/perineal hematoma, as well as blood at the meatus/introitus. Often radiographic

evaluation shows concomitant pubic rami fracture, symphysis separation, or posterior pelvic arch displacement. In posterior urethral injuries, rectal examination may reveal a pelvic hematoma or upward displacement of a distended bladder. Early management includes initiation of broad spectrum antibiotics, establishment of urinary drainage, and evaluation of the level injury. In boys initial evaluation of urethral injuries includes retrograde urethrocystography prior to any attempts at catheterization. The urethra is not instrumented if an injury is identified. In females, the urethra and the bladder neck are best evaluated by cystoscopy. Consideration should be given to possible coexisting rectal injuries in boys, which can present with certain pelvic fractures [14].

Treatment options include early, delayed, and late repair of injury. In children partial tears of the urethra heal better if permitted to do so spontaneously either over a urethral catheter or with placement of a suprapubic catheter. After 7–10 days a voiding cystourethrogram is carried out by instilling contrast through the suprapubic catheter or alongside the urethral catheter. If the wound has healed, the catheter is either clamped or removed and the child is permitted to void. If required, urethral reconstruction is generally delayed until the acute inflammatory process and hematoma have resolved. Typically the bladder is drained with either a suprapubic or urethral catheter. This allows time to evaluate the extent of the injury after the defect has matured. Multiple surgical options exist including primary end to end urethroplasty, continent urinary diversion, flap patch urethroplasty, and graft patch urethroplasty. The decision of appropriate surgical correction depends on location of the injury, length of the damaged segment, and function of the bladder neck.

Complications

Early complications include infection of the perineal/pelvic hematoma with associated extravasation of urine. Late complications include incontinence related to bladder neck/sphincter mechanism disruption, erectile dysfunction, and failure of repair. Management options for incontinence include artificial urinary sphincter, sling procedure or placement of a continent stoma using the Mitrofanoff principle. In the female population the need for continent diversion approaches 30 % [71, 72]. Erectile dysfunction (ED) is related to the severity of the initial injury. Severe dislocation of the prostatic urethra has a 70 % rate of ED. Failure of the initial repair can result in recurrent stricture disease, fistula formation, and severe debilitation as these patients may undergo multiple endoscopic and open surgeries.

Scrotal and Testicular Trauma

Trauma to the scrotum (Fig. 18.10) occurs infrequently and severe injuries are unusual because of the size and mobility of the pediatric testes. The mechanism of injury is compression of the scrotum against the inferior pubic ramus. Testicular torsion has a similar presentation and trauma has been known to result in torsion. The differential for the acute scrotum includes torsion of testicular appendages, varicocele, testicular torsion, epididymitis/orchitis, contusion of the scrotal wall and scrotal hematoceole with or without rupture of the testis.

Diagnosis

Physical exam findings typically include scrotal bruising and testicular discomfort. Imaging options include MRI or ultrasonography. Scrotal ultrasound is routinely available but is operator dependent.

Management

Indications for surgery include intra-testicular hematoma, ruptured testicle, or large hematoceole. If the testicle is ruptured or a large hematoceole is observed, exploration is

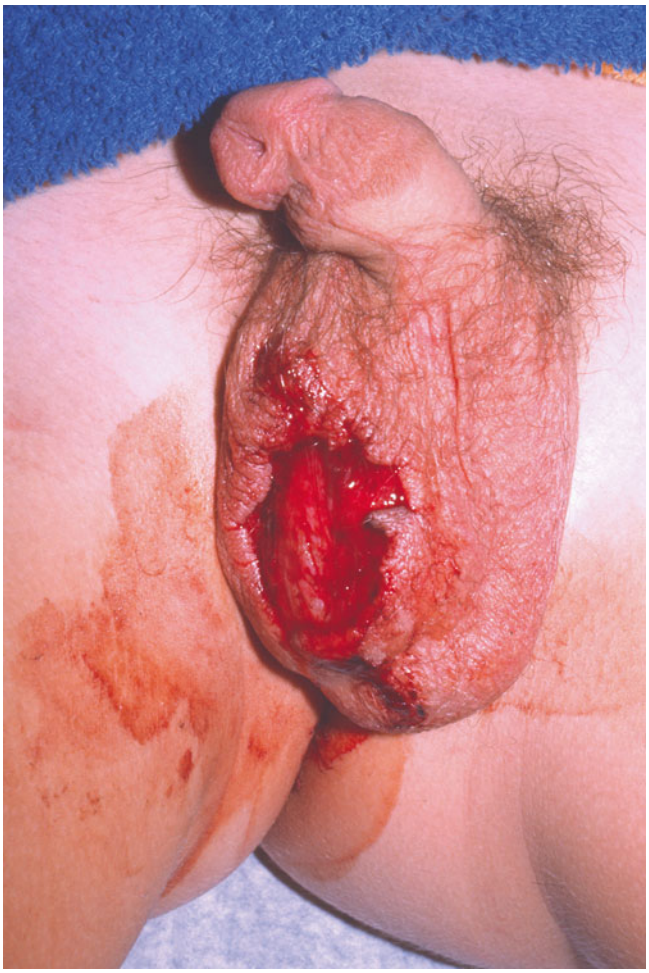

Fig. 18.10 A 14-year old male with scrotal injury after bike accident. The testis on the side of the laceration was not injured. The wound required operative debridement and closure

indicated to control bleeding, drain the hematoceole, and repair the tunica albuginea. Testicular exploration is also indicated if testicular torsion is suspected. Scrotal wall contusions without testicular injury should receive symptomatic treatment. Isolated scrotal wall hematomas are not amenable to drainage as the bleeding occurs between the layers of the scrotal skin and not in any potential space.

Penetrating injuries usually require debridement and repair if the testes are involved. Antibiotics are administered to avoid secondary infection. Delayed management increases the risk for testicular loss as well as creation of anti-sperm antibodies. The significance of which is unknown but thought to relate to decreased pregnancy rates [73].

Female Genital Trauma

Labial trauma is usually accidental as a result of athletics or activities on the playground however more serious injury can occur with penetrating trauma, or injury related to sexual assault. As discussed previously, thorough examination should be conducted for concurrent urethral or rectal lacerations. As such a rectal exam and urinalysis should be performed. The external urinary meatus may be inflamed but the female urethra is generally not injured. When necessary an examination under anesthesia may be required to completely identify vaginal, rectal and urethral involvement. Labial hematomas can be substantial, and my require catheter drainage of the bladder until the swelling subsides.

Sexual abuse must always be kept in mind when evaluating children with perineal injuries. Associated rectal trauma, in either sex, raises the index of suspicion. Additionally signs of parental neglect or non-urologic physical abuse should warrant investigation and notification of the appropriate personnel.

Penile Trauma

Penile injury is commonly the result of iatrogenic injury including circumcision. Other causes include zipper accidents (Fig. 18.11), animal attacks, hair tourniquet, and crush injury caused by the toilet seat. Circumcision can lead to excess removal of skin, thermal injury or urethral trauma. Typically, overzealous circumcision can be treated with wet to dry dressing changes with an acceptable cosmetic result. Gentle cleansing three times per day is usually the only treatment needed to prevent secondary infection. The management of severe injuries of the penis requires an individualized surgical approach which may involve microvascular reconstruction and the use of skin flaps or skin grafts.

Penetrating trauma typically requires exploration for evaluation of the urethral and corpus cavernosal injury.

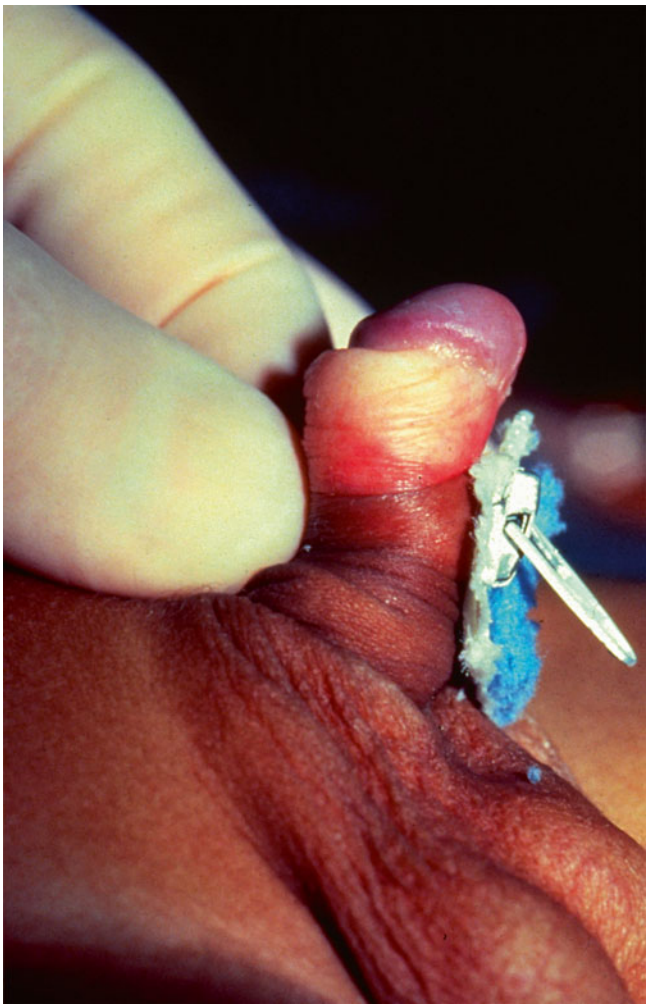

Fig. 18.11 A 7-year old male with zipper injury. In this case, the entire zipper was intact and removed. No urethral injury was present

Animal attacks can be severe and cause significant tissue loss. Initial management includes broad spectrum antibiotics, debridement, irrigation and repair based on the extent of injury. Blunt trauma to the perineum can result in priapism. Often this is a high flow non-ischemic state, as contrasted to the low flow ischemic state. Management in this setting is expectant as there is no foreseeable erectile dysfunction. In fact, treatment of high flow priapism with embolization techniques is more likely to cause erectile dysfunction.

Cases of amputation are rare including those seen as a result of caustic or electrical burns. At our institution we have had the unfortunate circumstance of observing injury from a lawnmower. In these devastating injuries the mainstay of therapy must be tissue preservation. This will allow the greatest option for reconstruction later. Immediate reconstruction of the penis is this setting is not advised.

Penile hair tourniquet is a rare event wherein a strand of hair encircles the penis and causes a strangulation ischemic injury. This can result in loss of tissue, urethral trauma, fistula

formation, or neurovascular damage. Treatment is to remove the offending strand, and evaluate the extent of damages, including urethra trauma, as delineated above. Consideration should be given to child neglect/abuse in these cases.

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Pediatric Orthopaedic Trauma

19

Charles T. Mehlman and Alvin H. Crawford

Abstract

Trauma patients that require pediatric intensive care unit services are likely to have significant orthopaedic injuries, and treatment of those injuries is increasingly likely to involve close coordination with orthopaedic surgery. This chapter on PEDIATRIC ORTHOPAEDIC TRAUMA focuses on the most common injuries that the pediatric intensivist will encounter in such situations. Available evidence that focuses on diagnosis, treatment, and clinical outcomes will be summarized.

Keywords

Orthopaedic injuries • Fractures • Trauma • Compartment syndrome

Introduction

The interface between the pediatric intensivist and the pediatric orthopaedic traumatologist is an all too common one. Orthopaedists are proud of the impact that modern advanced trauma life support programs have had on polytrauma patients [1]. Recent data from a large nationwide pediatric database review from the United States shows that out of about 8.5 million injured children per year, over 160,000 require hospitalization [2]. The most likely type of major operative procedure that pediatric trauma victims will undergo is orthopaedic surgery [3]. Half of all pediatric trauma victims will also suffer long-term sequelae from their injuries, and many will also suffer posttraumatic stress disorder [4, 5]. Childhood obesity has also emerged as a separate risk factor for extremity fractures and need for orthopaedic surgical intervention [6]. The rate and severity of pediatric musculoskeletal injury has seemed to keep pace with the increased popularity of extreme sports, motorized recreational vehicle use, and similar activities. All-terrain vehicle (ATV) injuries illustrate a particularly nasty subset of these pediatric trauma patients [7]. This chapter will review key aspects of pediatric orthopaedic trauma, focusing on current clinical evidence as it relates to pediatric critical care.

Pediatric Polytrauma

Pediatric polytrauma scenarios illustrate some of the most dangerous circumstances for patients and the most challenging for the larger critical care team. Only 170 verified pediatric trauma centers exist within the United States (41 states and the District of Columbia have one or more pediatric trauma centers) [8]. Even within those states that have pediatric trauma centers, many children continue to be treated at non-trauma center facilities [9]. Trauma remains the leading cause of death in children in the United States [10, 11].

Beyond the acute resuscitation phase, treatment decisions must be truly multidisciplinary in nature in order to optimize care. This has been termed the "collaborative model". Dr J Michael Dean (a pediatric intensivist) has said, "The surgeon should be a welcome partner in the PICU, and I think that the

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intensivist should put on surgical scrubs and join the surgical team in the operating room. Intimate knowledge of events in the operating room will improve the ability of the intensivist to care for the patient after surgery; likewise, knowledge of the ICU course will help the surgeon provide optimal care" [12]. A child with concomitant closed head injury, intra-abdominal injury, and pelvic fractures represents a prime example where such orchestration is indeed vital.

Head and neck related injuries (followed closely by extremity fractures) are the predominant injuries sustained by pediatric multiple trauma victims [7, 13]. Both short-term and long-term outcomes following pediatric multiple trauma are driven largely by head trauma severity [14–16]. Multiple studies have shown that early hypotension is strongly associated with worsened neurologic outcomes in head injured children [17–21]. Thus the potential value of orthopaedic surgical procedures aimed at fracture fixation must be weighed against the likelihood of deleterious neurologic effects secondary to hypotension [22]. Continuous intracranial pressure (ICP) monitoring during surgery, appropriate fluid management, and orthopaedic procedures aimed at minimizing blood loss are key elements to success.

Intra-abdominal [23] and pelvic injuries [24, 25] also present special concerns in the pediatric multiple trauma patient. The liver and spleen of children are less well protected due to proportionate size differences of the immature rib cage [26]. Nonoperative treatment protocols predominate [27] and necessitate certain activity restrictions that must be respected by the pediatric orthopaedic team [11]. A well-established relationship exists between thoracolumbar fractures (especially pediatric Chance fractures) secondary to lap belts and intra-abdominal injury [28–32]. When a seat belt sign (transverse lower abdominal linear ecchymosis) is present, more than 50 % of patients will have a confirmed intra-abdominal injury (including mesenteric or bowel injury, spleen and hepatic injuries) and at least 20 % of patients will require laparotomy [33]. A high index of suspicion must be maintained, communicated, and acted upon in a multidisciplinary fashion. A frequent scenario is that of initial recognition of the lap belt-related vertebral fracture followed by subsequent identification of intra-abdominal injury.

Femur Fractures

Femoral shaft fractures have consistently been the most common reason for pediatric orthopaedic in-patient admission at pediatric institutions [34, 35]. Femoral shaft fractures are also extremely common in pediatric multiple trauma victims [7, 10, 13, 27]. They represent disruption of the largest long-bone in the body and are accompanied by varying degrees of trauma to its surrounding soft tissue envelope. Significant amounts of blood can be lost due to femoral shaft fractures. However hemodynamic instability has been shown to not be due to isolated femoral bleeding, but rather it is indicative of more threatening abdominal or retroperitoneal injuries [36–39]. It has also been shown that hypotension may be an important indicator of head injury in pediatric patients [40]. Therefore, the likelihood of the need for pediatric general surgery or neurosurgery is much greater than the pediatric orthopaedist in these circumstances.

Near the time of initial presentation critical issues include splinting the fracture for purposes of pain control and limiting further soft tissue injury, ensuring adequate fluid resuscitation, and ruling out other organ system injury. Although a seemingly time-honored device, the Hare traction splint may be misapplied over 60 % of the time, thus making a case for proper training or expansion of the trauma splint armamentarium [41]. Under optimal conditions early fracture stabilization is desirable for purposes of pain control as well as speeding conversion to the rehabilitative phase. Separate from these goals, early (<24 h) versus late (≥24 h) surgery has not been shown to influence pediatric trauma outcomes [42, 43]. For patients too physiologically unstable for definitive surgery, bedside application of an external fixator will allow the patient to be mobilized for tertiary imaging *vis a vis* abdominal or neurologic injuries. Specific fracture stabilization methods will vary with the age of the patient, but most patients are currently treated surgically with intramedullary devices [44] (Fig. 19.1). Such femoral shaft fracture fixation techniques typically allow the patient to be up to a chair immediately and up with crutches or a walker (with protected weight-bearing) soon thereafter.

Distal femur growth plate fractures are a somewhat less common but much higher risk fractures when compared to femoral shaft fractures. Displaced physeal fractures of the distal femur are routinely associated with growth arrest rates in the 50 % range [45]. This is one of the most rapidly growing growth plates in the body, contributing 10 mm or more of femoral length each year. Therefore the consequences of growth disturbance can be devastating to a young child (Fig. 19.2). Anatomic reduction and stable internal fixation (often with a supplementary above knee cast) are the industry standard for treating these fractures. After satisfactory fracture healing these patients deserve radiographic screening for distal femoral growth arrest near the 6 months anniversary and 12 months anniversary of their injury.

Pelvic Trauma

Pediatric hip and pelvic trauma present a mixture of emergent, urgent, and late (follow-up) treatment issues. Emergent issues include those related to hemodynamic instability and resuscitation. It has been stated that the principles of management of pediatric pelvic disruptions should not differ

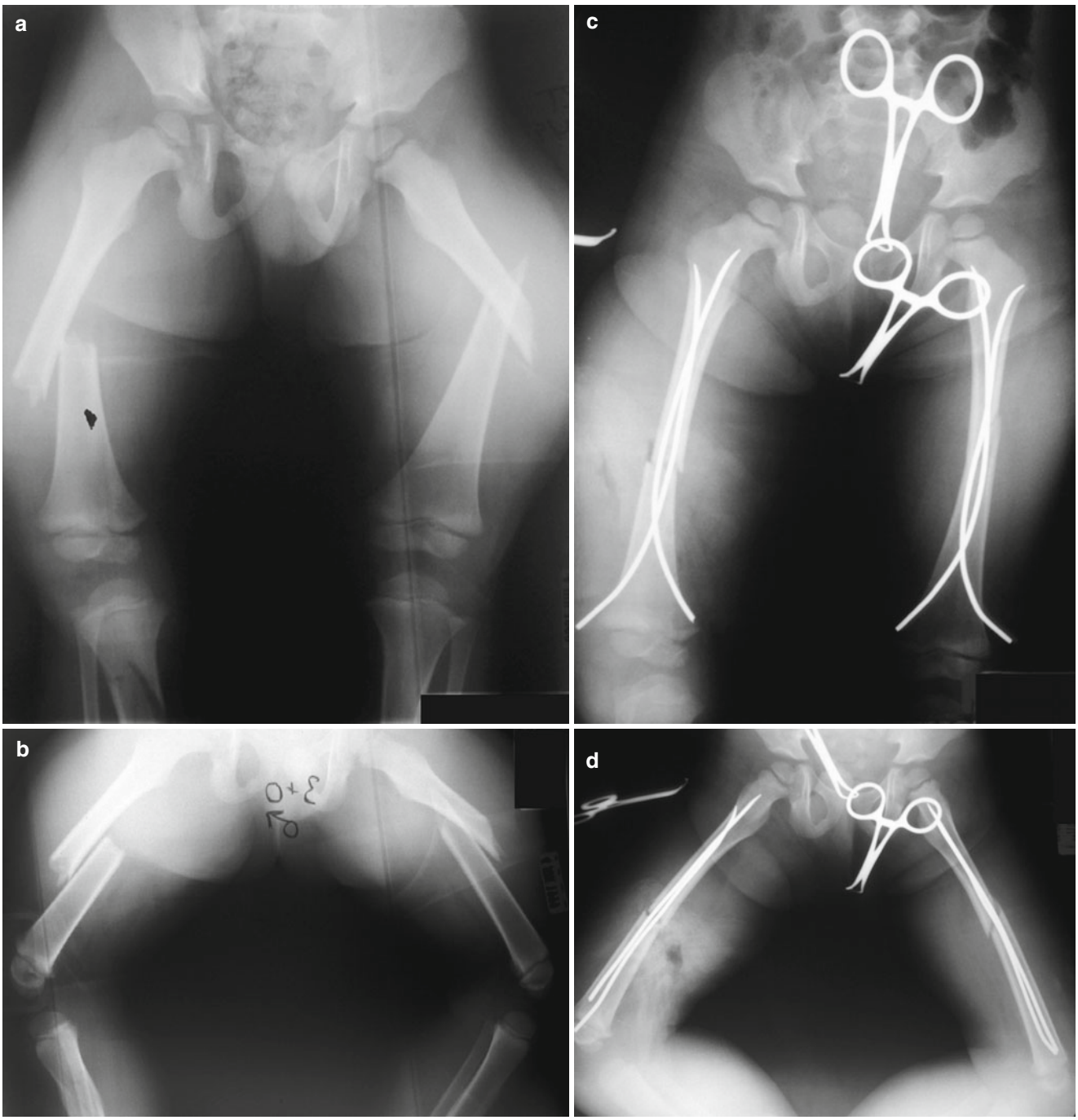

Fig. 19.1 A 3-year-old male multiple trauma victim whose injuries included bilateral femoral shaft fractures. (**a**) Initial injury AP radiograph demonstrating transverse right and oblique left femoral shaft fractures. (**b**) Initial injury lateral radiograph of both femur fractures (the right one was also a Type I open fracture). (**c**) Post-operative AP radiograph demonstrating elastic stable intramedullary nail (ESIN) fixation – also known as Nancy Nails as they were developed in Nancy, FRANCE. (**d**) Post-operative lateral radiograph – following such fracture stabilization the child may now be immediately transferred from bed to chair as indicated

greatly from adult principles [46]. Specifically, if pelvic instability is suspected, measures as simple as snuggly towel clipping a folded sheet around the pelvis may be very useful. If other explanations for hemodynamic instability have been ruled out [47, 48] and concern persists regarding displaced pelvic fractures, then a simple stabilizing pelvic external fixation frame should be applied [49, 50]. However beyond this acute phase some studies have shown that it is difficult to clearly establish that operatively treated patients enjoy better long-term clinical outcomes [51]. Other reports have

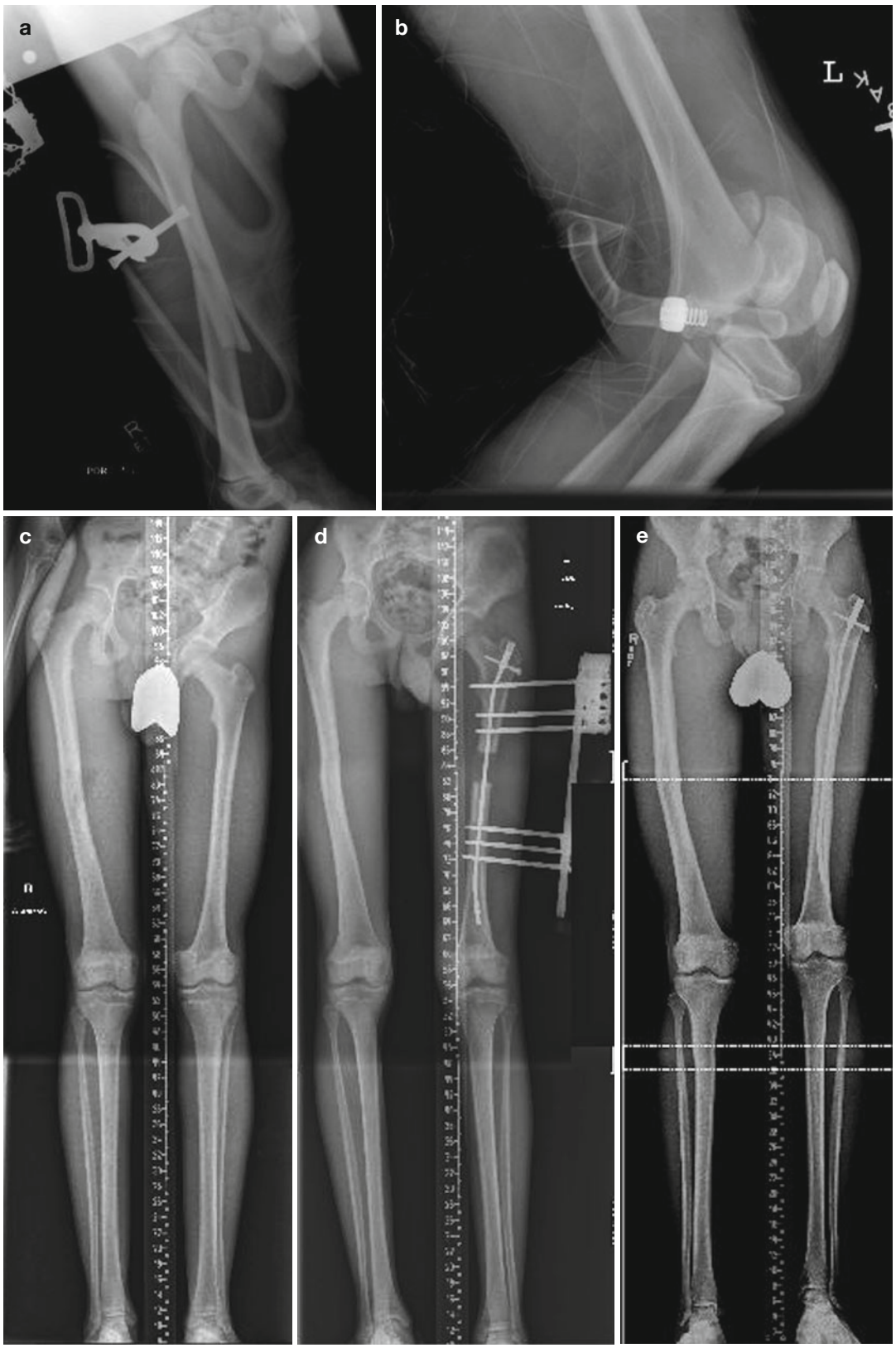

Fig. 19.2 A 9 years 10 months old male polytrauma victim who illustrates dramatic leg length discrepancy following growth arrest of left distal femoral physis (and later surgical equalization). (**a**) Injury radiograph showing right femoral shaft fracture. (**b**) Injury radiograph showing left distal femoral growth plate fracture. (**c**) Five year follow-up radiograph demonstrates 7 cm leg length discrepancy. (**d**) Lengthening left femur using monolateral external fixator and an intramedullary rod. (**e**) Two years post-op following lengthening

demonstrated favorable results with operative treatment of unstable pediatric pelvic fractures [52, 53]. Benefits include more rapid patient mobilization (through cast minimization) and normalization of pelvic bony anatomy (Fig. 19.3). Approximately 20 % of pediatric pelvic fracture patients will suffer long-term sequale such as growth abnormalities and difficulties with continence [54].

Urgent issues relative to pediatric hip and pelvic trauma include timely reduction of hip dislocations. Traumatic hip dislocations whose reduction is delayed greater than 6 h have been shown to have a 20 times higher risk of the potentially devastating complication called femoral head avascular necrosis [55]. This complication may not manifest itself until almost 1 year following injury. Late treatment issues include verification of proper pelvic growth via follow-up pelvic radiographs. Complications such as growth arrest of the triradiate cartilage (growth plate of the acetabulum) have been reported following such pelvic trauma [56–58]. Femoral neck fractures also may carry substantial risk of femoral head avascular necrosis in excess of 40 %. Older children and those with fracture patterns closer to the proximal femoral growth plate have been shown to be at higher risk. Based on the stability of the patient, rapid reduction and internal fixation is indicated for displaced femoral neck fractures.

Injuries to the Spinal Column

Few if any individuals have difficulty recognizing the gravity of phrases such as *She has broken her neck* or *His back is broken*. Based on national inpatient data, pediatric vertebral fractures are only the fifth most common orthopaedic injury, but they are associated with the highest mortality rates, the longest lengths of stay, and the highest total cost of care [35]. Isolated as well as multiple level bony or soft-tissue injury may occur in children [32, 59, 60], thus radiographic screening of the entire spine is often indicated. Motor vehicle related spine injuries predominate in the pediatric critical care setting [61, 62]. Important differences distinguish both the evaluation and treatment of pediatric spinal injuries from those of adults [63, 64]. Special attention has recently been paid to clinical clearance of the cervical spine in blunt trauma victims younger than 3 years of age [65]. Pediatric trauma surgeons from 22 institutions studied their combined trauma registry data and found four specific predictors with an accompanying weighted score of less than 2 identified children eligible for clinical clearance only (negative predictive value of 99.93 %) (Table 19.1).

An important clue to recognizing pediatric thoracolumbar vertebral fractures is the so called seat-belt sign. This ecchymotic stripe across the patient's abdomen occurs in the setting of isolated lap belt use and is most commonly associated with a pediatric Chance fracture (flexion-distraction injury usually at or near the thoracolumbar junction) [66]. A shoulder strap version of the seat-belt sign (in the region of the neck and clavicle) is also considered by some authors to indicate pediatric cervical spine fractures (Fig. 19.4) [67]. Special emergency transport measures are necessary when cervical spine injury is present or suspected in children less than 7 years of age. Herzenberg and his coauthors found that due to their disproportionately large heads, inappropriate cervical alignment was fostered when children were immobilized on standard adult-type backboards [68]. This pitfall can be avoided through the use of properly modified pediatric backboards (with a built-in recess for the head) or by elevating the remainder of the child's body with folded sheets or similar materials.

Another important difference between children and adults is the much higher likelihood of spinal cord injury without radiographic abnormality (SCIWORA) [69], which occurs in up to 38 % of all pediatric cervical spine injuries [62]. This injury pattern was recognized and the SCIWORA acronym coined in 1982 by Pang and Wilberger [70]. Magnetic resonance imaging classification of these injuries has been shown to be highly predictive of patient outcomes (Table 19.2) [71]. Modern treatment approaches to these children are associated with high rates of partial or complete neurologic recovery [72, 73] and high rates of successful non-operative (closed treatment/ external immobilization) treatment [74, 75]. When closed treatment efforts include halo-vest immobilization it must be remembered that children less than 2 years of age have less reliable bony purchase in their skulls and should receive a greater number of points of cranial fixation (usually 8–10 pins) [76]. Plain old spinal cord injury WITH radiographic abnormality is the more common circumstance, and surgical stabilization figures prominently in the treatment plan of children who survive these devastating injuries (Fig. 19.5).

Thoracolumbar injuries in children deserve additional discussion. Their association with intra-abdominal injuries must not be forgotten and proper multidisciplinary trauma evaluation is always appropriate [33]. These fractures may be divided into three simple groups: simple compression fractures (anterior wedging only with full maintenance of posterior vertebral body height), burst fractures (with compromise of posterior vertebral body height, varying degrees of retropulsion of fragments into the canal, and pedicle widening on AP radiograph), and flexion distraction injuries whose plane of disruption may be predominantly through the vertebral segment (the so-called Chance fracture) or through a varying degree of the periosteal sleeve/fibrocartilaginous boundaries of the vertebral segment. Simple compression fractures have been shown to have great potential for both healing and substantial remodeling when treated nonoperatively. Periosteal sleeve and fibrocartilaginous plane injuries have been nicely outlined by Paul Sponseller and they have

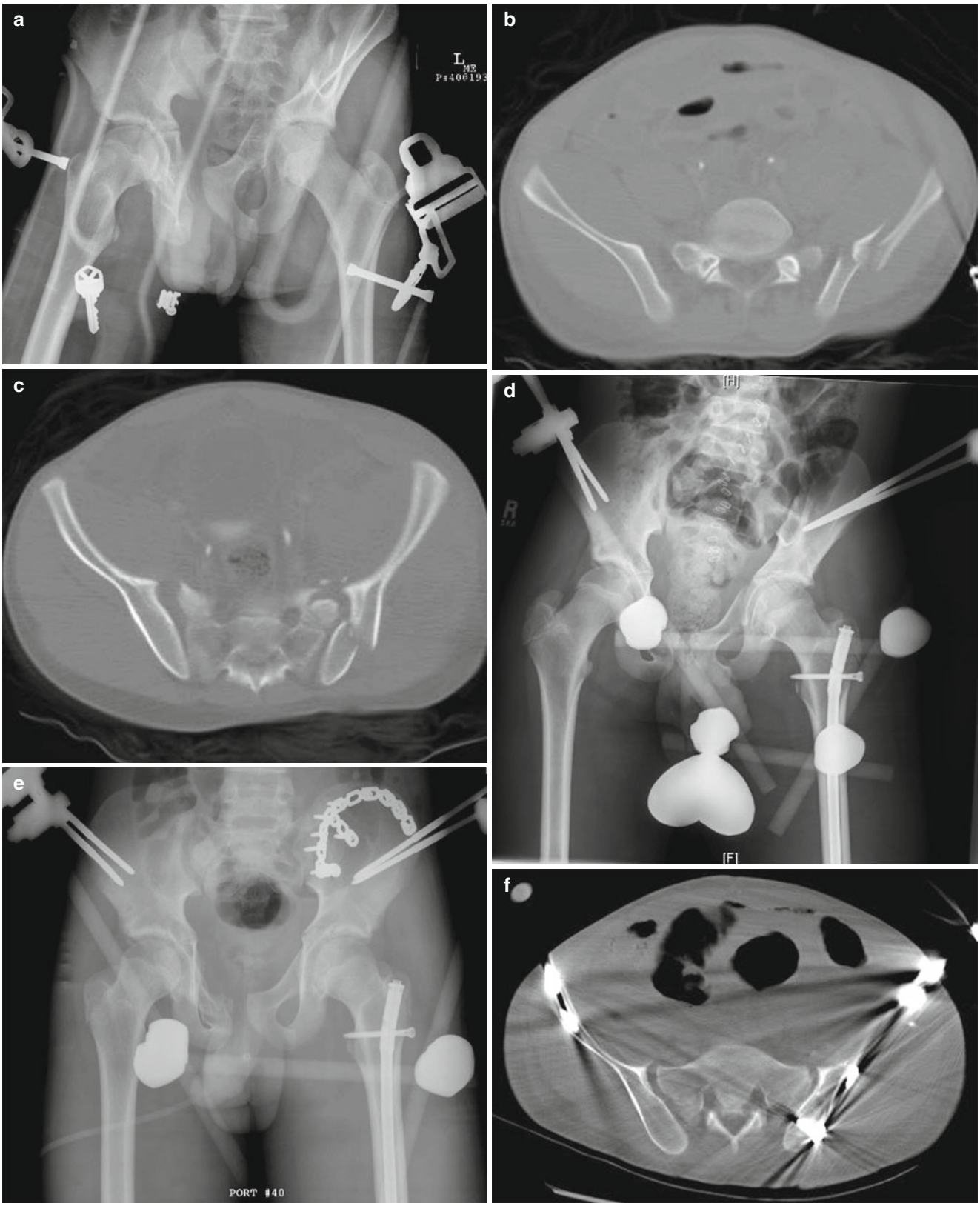

Fig. 19.3 Hemodynamically unstable 15-year-old male multiple trauma victim whose injuries included pelvic and acetabular injuries. (**a**) Initial injury AP pelvic radiograph demonstrating fracture dislocation of left sacroiliac joint as well as left ischial and acetabular fractures. (**b**) Computed tomography image demonstrating comminuted fracture of left ilem. (**c**) Computed tomography image demonstrating left sacroiliac joint involvement – this may be referred to as a pediatric crescent fracture. (**d**) AP pelvic radiograph 72 h later illustrating multiple procedures have been performed (emergently applied pelvic external fixator, emergent laparotomy, and locked intramedullary nail fixation of left femoral shaft fracture). (**e**) AP pelvic radiograph 12 days later following open reduction and internal fixation of left sacroiliac fracture-dislocation. (**f**) Post-operative computed tomography image demonstrating anatomic posterior reconstruction

Table 19.1 American Association for the Surgery of Trauma Clinical Clearance Scoring System for blunt trauma patients younger than 3 years of age

Variable	Points
GCS <14	3 pts
GCS_{EYE}=1	2 pts
MVC	2 pts
24-36 m/o	1 pt

Max score = 8 pts

Score <2 identifies pt eligible for clinical clearance only

a higher likelihood of successful nonoperative treatment due to the favorable healing potential of these tissues (as opposed to what is considered the less reliable healing of ligamentous tissue) [52]. Based on two recently published large series, the majority (60 %, 75/126) of these pediatric thoracolumbar fractures continue to be successfully treated via nonoperative methods [77, 78]. Figure 19.6 illustrates a striking example where surgery was necessary for a flexion distraction injury to the thoracolumbar spine with true fracture dislocation and complete permanent spinal cord injury.

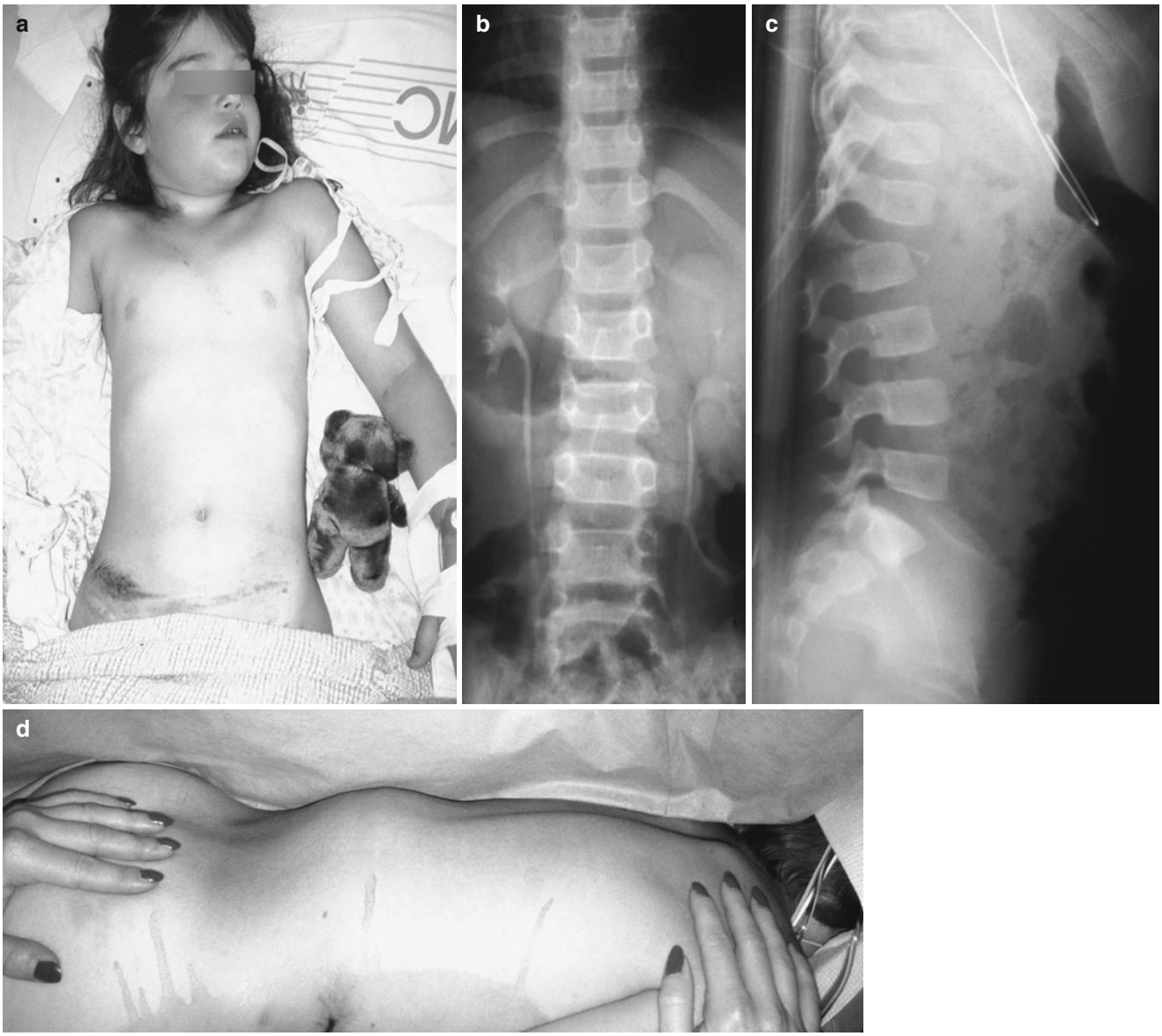

Fig. 19.4 Shoulder and Lap Seat-Belt Signs in a 5 years old female who suffered a Pediatric Chance fracture. (**a**) Clinical photograph showing ecchymotic stripe along lower abdomen – this is the seat-belt sign (she also had a shoulder harness on, which left a mark on her neck, but there was no cervical injury). (**b**) AP radiograph of thoracolumbar spine demonstrating classic transverse plane pedicle fractures of a pediatric Chance fracture (L-2 in this case). The IVP was normal. (**c**) Lateral radiograph of thoracolumbar spine demonstrating displaced L-2 pediatric flexion-distraction Chance fracture (note marked angulation between bodies of L-1 and L-2). (**d**) Clinical photograph demonstrating kyphotic deformity localized to the thoracolumbar junction. Note the residual of the betadine prep following the bowel repair

Table 19.2 MRI classification of SCIWORA

Class 1	Complete transection	All fail to recover
Class 2	Major hemorrhage	All fail to recover
Class 3	Minor hemorrhage	40 % improve to mild
Class 4	Edema only	70 % improve to mild, 25 % normal
Class 5	Normal	All make complete recovery

Adapted from Pang [71]. With permission from Wolters Kluwer Health

Compartment Syndrome

Compartment syndrome represents a limb-threatening pediatric orthopaedic emergency in which adequate tissue perfusion is compromised by local pressure differentials. Failure to recognize and treat it in a timely fashion may result in a withered and useless limb (Volkmann's ischemic contracture) or in rare cases even necessitate amputation. Compartment

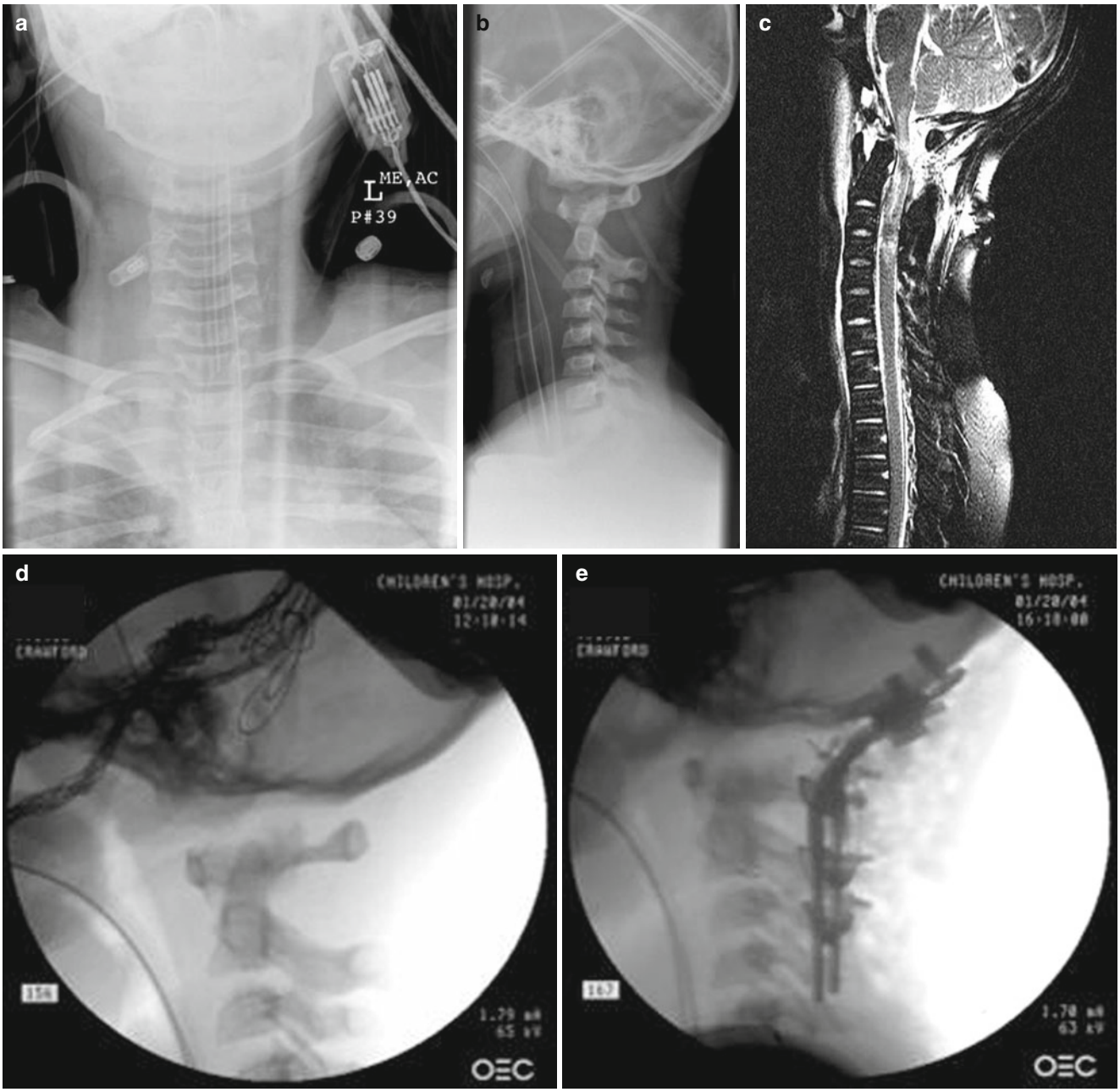

Fig. 19.5 A 9-year-old female MVA victim with occipito-atlanto, axial dissociation. She was quadriplegic on admission. (**a**) AP cervical spine radiograph. (**b**) lateral cervical spine radiograph showing C1–C2 dissociation and posterior displacement of the dens. (**c**) T-2 weighted sagittal MRI demonstrating spinal cord transection and significant soft tissue (ligamentum nuchal injury. The injury is below the ring of C1). (**d**) Fluoroscopic lateral c-spine image at the time of halo- assisted reduction. (**e**) Fluoroscopic lateral c-spine image demonstrating restoration of occipitocervical alignment with stable internal fixation. (**f**) Post-operative lateral cervical spine radiograph taken in halo-brace

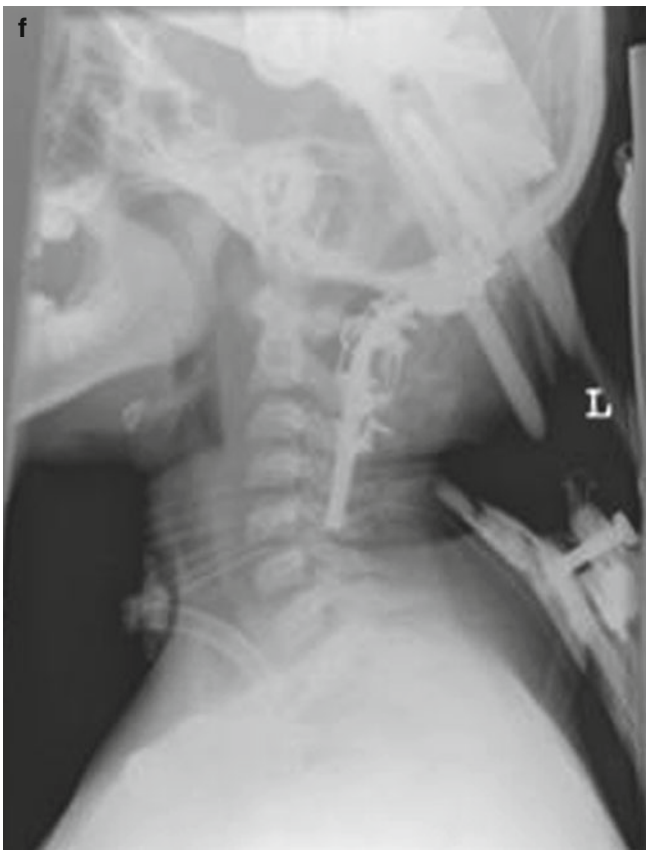

Fig. 19.5 (continued)

syndrome in children most commonly occurs in the setting of tibial shaft fractures (either open or closed) followed by forearm and elbow fractures [79–81]. A high index of clinical suspicion must be maintained in these instances. Pain out of proportion to the injury is the most important finding in alert communicative patients, but when dealing with tracheally intubated or obtunded patients the only clue may be tense compartments on physical examination. Increasing analgesia requirements in a child with an extremity injury has been suggested as a particularly important early sign of impending pediatric compartment syndrome (preceding other later findings by more than 6 h) [82, 83]. Special concern must also be exercised in a child who has suffered peripheral nerve injury as they may be deceptively comfortable despite a full-fledged compartment syndrome.

Three additional situations that may be encountered in the PICU also bear special mention. An increasing number of hand compartment syndromes have been reported secondary to intravenous fluid infiltration into subcutaneous tissue [84, 85]. The reported cases have several recurring features: younger patients (often less than 1 year of age), presence in an intensive care unit setting when the complication occurred, and normal intravenous pump alarms failed to function properly. Another special situation is that of the PICU patient who is receiving epidural analgesia. Efforts should be taken to avoid dense motor and sensory blockade in order NOT to mask an important early sign of compartment syndrome: pain out of

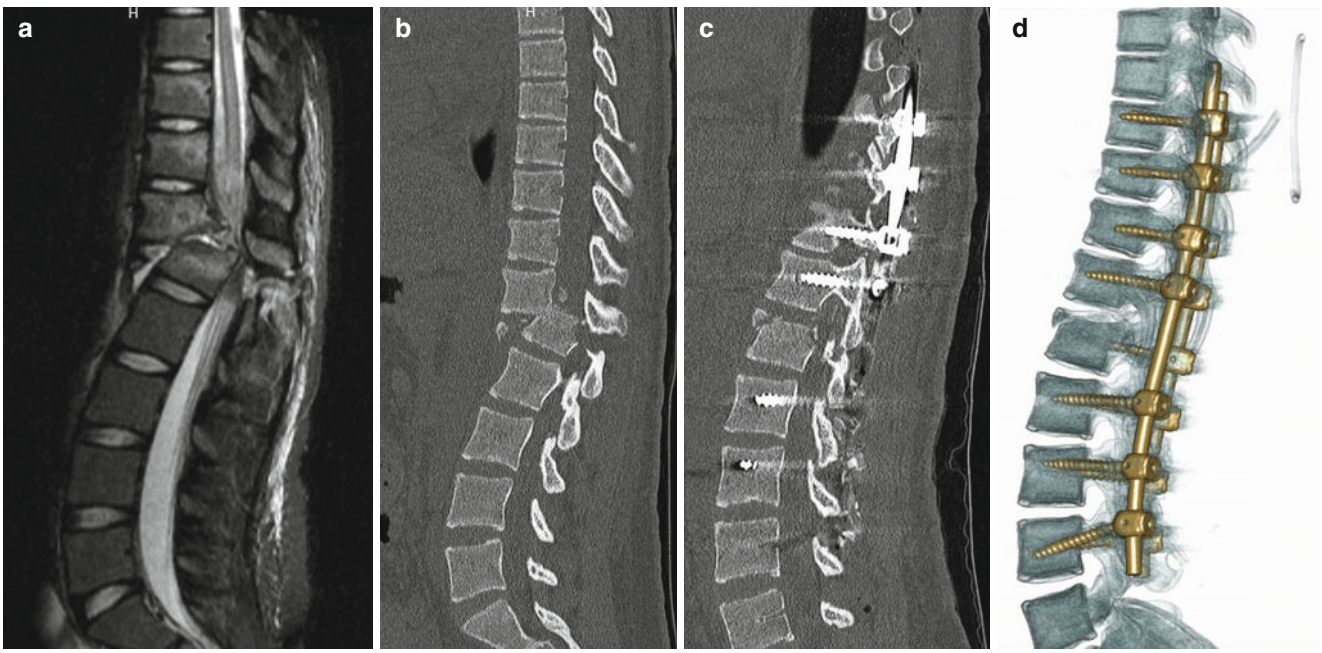

Fig. 19.6 A 14-year-old female victim of an ATV accident. (**a**) Pre-op MRI. (**b**) Pre-op CT. (**c**) Post-op CT. (**d**) Post-op 3-D CT (Case courtesy of Eric J. Wall, MD)

Table 19.3 Gustilo open fracture classification

Type I	Small relatively clean open wound less than 1 cm in size (often due to an "inside out" protrusion of the bone through the soft tissue envelope)
Type II	Larger wound usually between 1 cm and perhaps 10 cm (extensive deep soft tissue damage is not present)
Type III	These injuries have larger overall wounds and a greater degree of devitalized tissue and are subdivided into A, B, C…
A	Wound usually greater than 10 cm – but with sufficient preservation of local tissue (including periosteum) that flap coverage in not necessary
B	Classic type III wound size but with additional periosteal stripping/devitalization such that flap coverage is usually necessary
C	Classic type III wound size plus major vascular injury that requires repair in an effort to salvage the limb

proportion to the injury [86]. Finally, compartment syndrome concern exists regarding the increased use of peripheral nerve and regional blocks in children. Instances of compartment syndrome following such nerve blocks used in trauma surgery and elective surgery have been reported in adults [87, 88].

Clinical suspicion alone may be enough for experienced pediatric orthopaedic traumatologists to perform appropriate compartment releases (fasciotomies). In other instances the clinical decision making process is greatly facilitated by formal compartment pressure measurement using either commercially available devices or comparable pressure measurement tactics. Two compartment syndrome decision-making philosophies may be encountered in clinical practice. One commonly accepted practice is that compartment pressures in the 30–45 mmHg represent absolute values that will trigger surgical compartment release. The other occurs when the relative difference between compartment pressure and diastolic pressure is less than 30 mmHg. Thus with the second philosophy (interpretation within the context of the patient's blood pressure) the threshold for compartment release may be somewhat higher in a normotensive patient and significantly lower in a hypotensive patient.

Open Fractures

In the PICU, open fractures (referred to as compound fractures in the past) may range from subtle to grotesque. What they all have in common is that fracture hematoma communicates with the outside world. In one large series the two most common types of pediatric open fractures were the forearm and tibia [89]. The principles of open fracture management focus on irrigation and debridement (often serially) until only viable tissue remains. Modern pediatric internal fixation techniques have largely replaced the external fixators of yesteryear [90]. The Gustilo classification has stood the test of time with respect to usefully segregating open fractures into clinically meaningful groups (Table 19.3). Classic orthopaedic teaching has stated that all open fractures require surgical treatment within 6 h or less following injury. More recent data has challenged this contention in that no increased risk of open fracture complications was found in the setting of pediatric Type I and II injuries treated within 24 h of injury [91, 92]. Type III injuries were poorly represented in these studies and thus traditional urgent irrigation and debridement protocols are considered most appropriate.

Orthovascular Trauma

Displaced fractures may also be associated with vascular injury that threatens limb viability. The amazing thing is not that this occurs, rather that this does not occur more often. Fractures adjacent to major arterial branching areas seem to be at greater risk, as large National Trauma Databank information indicates that the most common pediatric vascular injury of the upper extremity is the brachial artery (22 % of cases, 148/684) and the most common vessels of the pediatric lower extremity to be injured involve the popliteal vasculature (11 % of cases, 73/684) [93]. The majority of these arterial injuries occur in conjunction with adjacent displaced fractures. Up to 10 % of such pediatric vascular injury patients may end up with an amputation [94]. It is also clear that individual institutional experience with such vascular injuries is rare (even at busy tertiary pediatric trauma centers). Multidisciplinary protocols (reviewed and approved by appropriate stakeholders) are thus indicated in order to optimize outcomes for such "rare event-high potential for morbidity" scenarios [94].

Absent distal extremity pulses (defined as medical personnel cannot palpate a pulse) are simply not normal [95]. Capillary refill may seem to be well-maintained, but a non-palpable distal pulse means that the patient has an abnormal vascular examination. Supracondylar humeral fractures are the most common pediatric elbow fracture, and approximately 10–15 % of the time they present without a palpable radial pulse. Following reduction and internal fixation, close to half of patients will remain pulseless and greater than 70 % of those patients have been shown to have true arterial injury [96]. Vasospasm may be the explanation for such abnormal vascular examinations, but this is true in the minority of cases (most commonly vasospasm afflicts those less than 10 years of age) [97]. Patients with abnormal vascular examinations deserve aggressive evaluation and surgical intervention as indicated. Doppler duplex imaging

of suspected vascular trauma is a well established tool that has demonstrated both sensitivity and specificity of 95 % or greater [98], and surgical exploration and repair is indicated if inadequate distal perfusion is identified.

Clavicle Shaft Fractures and Rib Fractures

Within recent years clavicle shaft fracture care has experienced a true sea change in the orthopaedic world. Based on a reasonably large randomized clinical trial conducted by the Canadian Orthopaedic Trauma Society, lower nonunion rates and improved upper extremity function were demonstrated in adults whose clavicle shaft fractures were treated with plate and screw fixation [99]. No similar Level I pediatric data exist, but certain Level III and IV data has shown that clavicle shaft surgery can be performed reasonably safely [100] and functional outcomes may be achieved 4 weeks sooner with surgery as compared to nonoperative treatment. It has also been shown that the vast majority of clavicle growth has been completed by 9 years of age in girls and 12 years of age in boys [101]. All of this information needs to be taken into consideration along with the accepted trauma principles of fracture stabilization to aid patient management and rehabilitation when contemplating the relative risks and benefits of clavicle surgery.

Another provocative trauma topic has been that of surgical stabilization of rib fractures. Indications for operative management of adult rib fractures have evolved and include: flail chest (usually defined a unilateral fracture of four consecutive ribs), open fractures, and to decrease acute pain and disability [102]. A growing number of adult series have documented both short-term (shorter required period of ventilator support) and long-term (better pulmonary function at 6 months) outcomes following surgical stabilization of rib fractures [103, 104]. A recent prospective series has also confirmed lower pain levels in operatively treated adult patients [105]. The risk of pediatric mortality has been shown to be directly proportional to the number of rib fractures a child suffers [106]. The potential role for surgical stabilization of rib fractures would appear to be in the setting of older adolescents and teenagers.

Conclusion

These trauma patients will continue to challenge both the pediatric critical care intensivist and the pediatric orthopaedic traumatologist for the foreseeable future. At some future date perhaps a combination of injury prevention programs, legislation, and law enforcement will threaten the job security of those who care for such pediatric trauma victims. Until that time we must continue to refine the systems we have designed to care for these children. We are not doing such a bad job so far, as the positive impact of pediatric trauma centers is hard to deny [107, 108]. We must also continue to care for these children in a holistic fashion, demonstrating appropriate knowledge of, respect for, and coordination of the skills offered by the various disciplines poised to lend their aid.

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Pediatric Burns

20

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Abstract

Burns are a common injury in children, primarily occurring during the first 5 years of life. Advances in burn care such as fluid resuscitation, prompt wound excision and coverage, and infection control have substantially improved survival and diminished complications after burns. This has shifted focus to providing greater psychological support to survivors and preventing disfiguring scarring. This chapter will provide an overview of these and other major elements of burn care, with special emphasis on challenges encountered with children. It will begin with a discussion of burn classification, which is integral to guiding treatment choices. It will then describe multiple aspects of burn treatment ranging from initial management and fluid resuscitation to the final stages of rehabilitation. This discussion will include the diagnosis and treatment of inhalation injury, a primary cause of mortality after burns, as well as the surgical management of burn wounds, wound closure alternatives, antimicrobial treatments, and the unique nutritional needs of the burn population. The chapter will conclude with a description of commonly seen complications of burns and the benefits of exercise and psychological support in long-term recovery from these injuries.

Keywords

Fluid resuscitation • Infection • Smoke inhalation • Nutrition • Wound • Rehabilitation

Introduction

Burn injury is the third most common cause of mortality secondary to injury in children, with the majority of burns sustained by those under 5 years of age [1]. Pediatric burn injuries present a unique management challenge secondary to the specific physiologic and psychologic needs of children. Approximately 60 % of childhood burn injuries are scald burns caused by accidental exposure to hot liquids or intentional exposure and immersion in hot substances by another individual. Flame burns account for approximately 10–25 % of pediatric burns and are most commonly observed in children 10–14 years old. Contact burns account for 10–30 % of burn injuries in children and are most common in children less than 5 years of age. Burns in older children frequently occur during risk-taking activities, while playing with fireworks, and when using flammable substances. Although children can survive large burns and achieve an

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acceptable quality of life, those less than 5 years of age are more likely to be hospitalized and succumb to injury – especially if they are from a low socio-economic background [1]. Herein we describe the pathophysiology of burns in the pediatric patient to facilitate the early identification of management issues and to guide the appropriate treatment of burn injuries in this population.

Classification of Burn Injuries

Determination of the extent of burn injury is essential for the proper care and treatment of burned patients. Adult patients and children over the age of 15 years are assessed using the "rule of nines" (Fig. 20.1), which attributes 9 % of the total body surface area (TBSA) to each of the following: head, each upper extremity, each anterior and posterior lower extremity, and the superior and inferior anterior and posterior torsos [2]. In the pediatric population values assigned to specific body regions change with age to account for the disproportionate growth of the head and extremities, making the rule of nines inadequate. Children can more accurately be evaluated using a modified rule of nines (Fig. 20.2) that attributes the following percentages to various aspects of the body: head and neck (18 %), each lower extremity (15 %), each upper extremity (9.5 %), the anterior torso (9.5 %), and the posterior torso (16 %) [3]. This estimation accounts for the larger cranial surface area and lower extremity area in children compared to adults. Burn centers have developed modified Lund-Browder diagrams for all age groups with attributable percentages to specific body regions based on age and size [4]. These diagrams should be completed during the initial patient evaluation and should be adjusted as the burn wounds demarcate over time.

A standard classification system is used to determine the depth of burn injury. First degree burns are limited to the epidermis. Second degree burns involve the epidermis and dermis (either superficial or deep dermis), and third degree burns are full thickness injuries involving the epidermis and dermis, with extension into the subcutaneous tissue. Fourth degree burns are full thickness burns extending to muscle or bone.

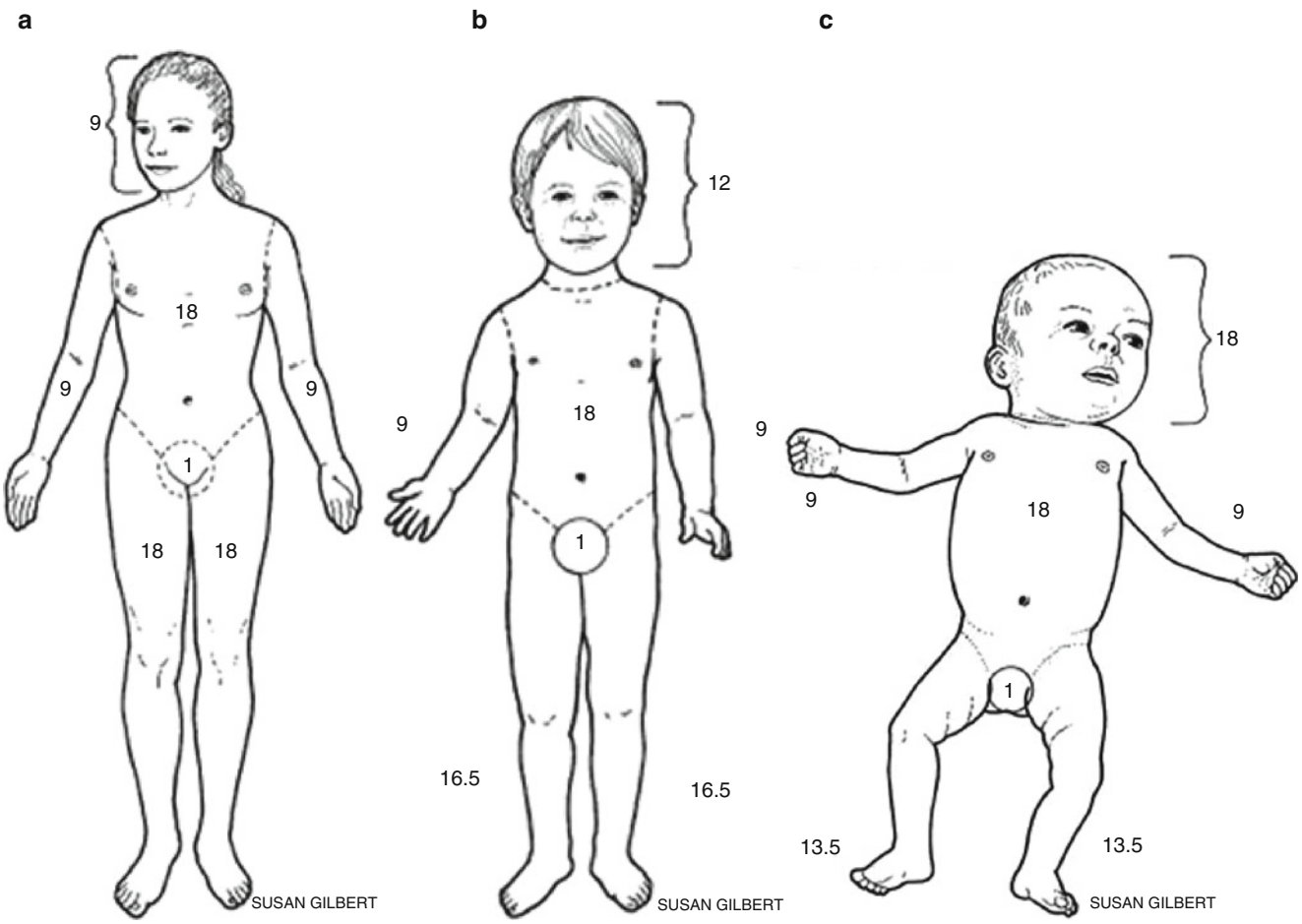

Fig. 20.1 Rule of nines for (**a**) adolescents, (**b**) children, and **c** infants (Reprinted from Foltin et al. [40]. With permission from Center for Pediatric Emergency Medicine (CPEM))

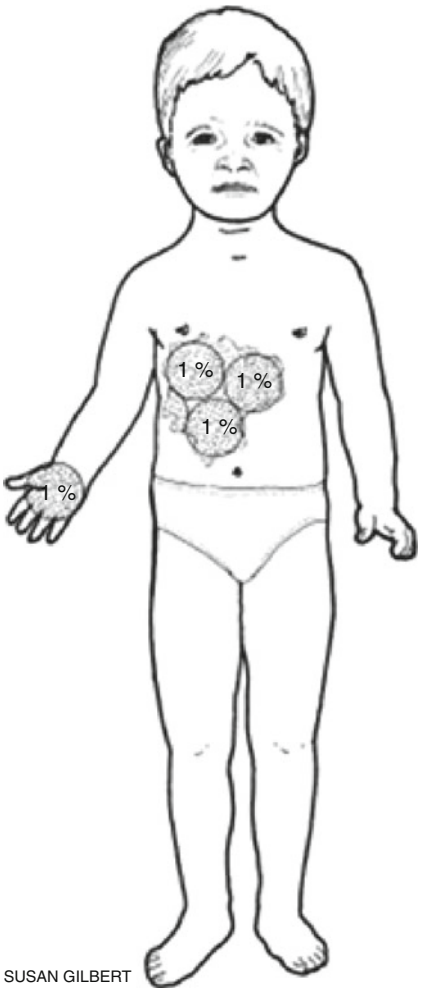

Fig. 20.2 Rule of palms (Reprinted from Foltin et al. [40]. With permission from Center for Pediatric Emergency Medicine (CPEM))

First degree burns are confined to the epidermis and do not blister or lead to scar formation; common first degree burn injuries are sunburns and minor scald injuries. Patients typically present with associated erythema, mild pain, and minimal edema and tenderness to palpation. These injuries will typically heal without further intervention. Standard treatment for these burns includes topical moisturizers and pain management with oral non-steroidal anti-inflammatory drugs (NSAIDS). These injuries typically cause the epidermis to peel and superficially heal within 3–6 days of time [3, 5, 6].

Second degree or partial thickness burns extend into the dermis and are further divided into superficial and deep components. *Superficial partial thickness burns* involve the papillary dermis and present with clinical findings of a moist surface, blanching erythema, blisters, and tenderness. Patients report extreme pain with these injuries. *Deep partial thickness burns* involve the reticular dermis, and examination demonstrates a wet wound with hemorrhagic blisters, white or red appearance, and less blanching erythema. In the pediatric population, deep partial thickness burns frequently progress into third degree burns over the course of several days. Superficial partial thickness burns are usually the result of exposure to hot liquid and flash flame burns. These wounds often re-epithelialize within 7–21 days depending on the extent of remaining epidermal structures such as sweat glands and hair follicles. Slight skin discoloration typically occurs after healing. Deep partial thickness burns take longer to heal (14–35 days) with severe scar formation occurring following loss of the dermal layer. Those wounds that do not heal within 3 weeks require excision and grafting for definitive management and minimization of contracture and scar formation [3, 5, 6].

Third degree, or full thickness, burns extend through the epidermis and dermis to the subcutaneous fat. These injuries are characterized by a white, brown, or cherry red appearance, a stiff eschar that is non-blanching and insensate, and a dry and leathery appearance. Tenderness to palpation does not occur due to the loss of innervation within the dermis. These wounds should be excised and grafted early to minimize infection and hypertrophic scar formation [3, 5, 6].

Fourth degree burns extend to the nerves, fascia, tendons, muscles or bones, and are visibly stiff, brown, and charred in appearance, and they demonstrate the presence of thrombosed vessels. Fourth degree burns usually occur secondary to high-voltage electricity or prolonged flame exposure. Patients do not complain of pain, and the wounds are non-tender to palpation with demonstrable loss of sensation. These wounds will not heal without skin grafting [3, 5, 6].

The extent of local tissue injury following a burn can be evaluated by identification of three concentric zones of injury: the zones of coagulation, ischemia (stasis), and hyperemia. The zone of coagulative necrosis occurs at the center of the burn; damage within this region is irreversible. This area usually has the most direct contact with the heat source. The surrounding zone of ischemia can become necrotic (or undergo conversion) dependent upon the depth of injury and reduction in microcirculation within the first 24–48 h. Management of this region with inhibitors of endogenous vasoconstrictors to attenuate the inflammatory process is crucial to limiting the extent of the burn injury. Immediately after injury, the outermost zone of hyperemia develops a transient increase in perfusion secondary to the vasodilatation of the inflammatory process surrounding the burn wound. This area contains viable tissue and should recover within 7–10 days [5–7].

Tissue damage is dependent on the burn mechanism. Scald, flame, and contact burns induce cellular damage and coagulative necrosis via the transfer of energy from the heat source. Chemical and electrical burns cause tissue damage via the combination of direct contact-induced damage and heat transfer [6]. When a thermal injury is sustained, inflam-

matory cells are activated, causing the release of mediators including cytotoxic cytokines and free oxygen radicals. The activities of these mediators lead to alteration of the cell membrane lipid bilayer with resultant tissue necrosis. Formation of microthrombi, along with cycles of ischemia and reperfusion, causes a further reduction in tissue perfusion. Young patients are particularly susceptible to deep burn injuries because their skin is thinner, and their blood supply and dermal appendages are less developed, decreasing heat dissipation [5].

Initial Management and Evaluation

Burned clothing should be immediately removed and residual flames extinguished. Chemically saturated clothing should also be removed and residual chemicals on the skin brushed off, or if the chemical is a liquid, washed away with copious irrigation. The burn wound should then be covered with a dry clean dressing, and patients should be kept warm to minimize hypothermia and maintain core body temperature. Topical antimicrobials should be avoided until after the patient has been thoroughly evaluated [5]. As with a trauma patient, the initial evaluation of a pediatric burn patient involves an orderly, systematic approach allowing for the identification and initial stabilization of potential life-threatening injuries, followed by a thorough evaluation of the extent of injury. This assessment should follow the guidelines of the American College of Surgeons Committee on Trauma and the Advanced Burn Life Support course of the American Burn Association. The first step in the primary survey is the assessment of the airway. Burns to the head and neck, particularly those suggestive of inhalation injury with singed nasal hairs, carbonaceous sputum, and tachypnea may result in upper airway edema requiring immediate tracheal intubation. Patients with massive burns may initially lack respiratory compromise, but airway edema may ensue following resuscitation with several liters of fluid.

Once the airway is secured, the breathing status of the patient can be determined by evaluating the exposed chest for adequate rise and fall, listening for equal breath sounds bilaterally, or determining CO_2 return in intubated patients. In patients who have charred or edematous extremities, circulation can be indirectly measured using the pulse rate [3, 6, 8]. The secondary survey allows for a careful examination of the entire body. For small burns in an outpatient setting, abuse should be considered if the mechanism of injury is questionable or suspicious. Emergency response personnel should be interviewed in the emergency department to obtain the mechanism of injury and other relevant clinical information [3].

After the primary and secondary surveys are completed and the patient stabilized, the burn wound should be evaluated for extent, depth, and circumferential aspects. Patients with inhalation injuries, large burns, or burns containing circumferential or near circumferential components should be transferred to a dedicated burn center, as these patients will need special monitoring and may require escharotomy within 12–24 h after injury [3].

Hospital Admission

Burn patient outcomes have improved greatly within the last several decades. This is due to improvements in the management of burn patients by dedicated burn centers with experienced personnel and established treatment protocols. Concern remains, however, that a significant number of patients are not being referred to regional burn centers despite meeting ABA referral criteria. Because significant long-term sequelae such as loss of function, psychosocial disability, and hypertrophic scar formation can occur, appropriate referral and treatment by a multidisciplinary team is critical to long-term outcome. Timely referrals to burn centers lead to reductions in patient morbidity and mortality, the length of hospital stay, and the associated costs of treatment [9]. Patients who meet the following criteria set by the American Burn Association should be referred for admission to a regional burn center: (modified from [9]):

- Partial-thickness burns greater than 10 % TBSA
- Burns that involve the face, hands, feet, genitalia, perineum, or major joints
- Third-degree burns in any age group
- Electrical burns, including lightning injury
- Chemical burns
- Inhalation injury
- Burn injury in patients with preexisting medical condition that could complicate management, prolong recovery, or affect mortality
- Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be initially stabilized in a trauma center before being transferred to a burn unit.
- Burned children in hospitals without qualified personnel or equipment for the care of children
- Burn injury in patients who will require special social, emotional, or long-term rehabilitative intervention

Fluid Resuscitation

Burn injury leads to systemic capillary leak, which can lead to massive fluid redistribution and loss. Acutely burned patients require aggressive resuscitation for the first 24–48 h after injury. Burns <15 % TBSA can be resuscitated orally. Intravenous (IV) access should be established immediately

for administration of fluids in patients (adults and children) with burns >15 %TBSA and in infants with >10 % TBSA burns. Access should be obtained early postburn, even though such access may be difficult to secure and may have to be placed in burned tissue. Ideal access in pediatric patients can be obtained via the placement of two large-bore catheters, an intraosseus catheter, or a central venous catheter if peripheral access is not available [10, 11]. Early in the resuscitation phase, release of inflammatory mediators such as histamine, prostaglandins, and leukotrienes increases vascular permeability, which further worsens capillary leak and tissue edema.

Isotonic crystalloid solutions, such as Lactated Ringers, and normal saline serve as the first line fluid replacement following burn injury [5]. Several formulas and specific infusion rates based on the burn size and patient weight can be used for management of patients during the first 24 h of burn injury. These rates should be adjusted towards an adequate end point of resuscitation with caution to avoid over-resuscitation of the patient. The resuscitation effort is often based on adequate urine output, which is considered to be predictive of an adequate glomerular filtration rate, renal blood flow, and cardiac output. Additional end points such as blood pressure, capillary refill, and mental status should also be followed.

The Parkland formula (4 mL/kg/%TBSA burned for 24 h) with half of the volume given in the initial 8 h post-burn is commonly used to guide the resuscitation effort in adults and older children, with fluids being adjusted to maintain an hourly urine output of at least 50 mL/h [12]. Resuscitation in children weighing less than 20 kg can be achieved using the Galveston Shriners formula, which is based on body surface area instead of weight to account for the greater net fluid losses in pediatric patients due to their smaller body weight to surface area ratio. Children have a small body weight to body surface area ratio, which results in proportionally greater net fluid losses. Body surface area (BSA) is calculated from height and weight [BSA = height (cm) $^{0.725}$ × weight (kg) $^{0.425}$ × 0.007184]. Lactated Ringers is then administered at 5,000 ml/m^2 TBSA burned plus 2,000 ml/m^2 TBSA for maintenance fluid given in the first 24 h with half of this volume administered in the first 8 h post-injury [13, 14]. Following the initial 24 h of injury, 3,750 ml/m^2 TBSA burned (or open) plus 1,500 ml/m^2 TBSA (for maintenance) is given. Dextrose is added to the fluid in children less than 2 years of age to account for limited carbohydrate reserves and expected hypoglycemia. Pediatric burn patients have a higher urine output target secondary to a larger surface area to body weight ratio, with a target of 1 mL/kg/h in children and 2 mL/kg/h in infants. Renal medullary concentrating ability is also decreased in children compared to adults. Resuscitation efforts should be goal directed to specific endpoints; over-resuscitation of patients leads to associated complications with increased morbidity and mortality. Pulmonary edema, right heart failure, and abdominal compartment syndrome can result from over-resuscitation. Abdominal compartment syndrome is a dire consequence of large volume resuscitation and often requires laparotomy to relieve pressures and restore adequate end-organ perfusion [6, 15]. Progression to laparatomy is associated with a mortality rate of over 50 % [15].

Patients with inhalation injury, electrical burns, and a delay in resuscitation required greater amounts of resuscitation fluid [16]. These patients are at risk of developing myonecrosis and rhabdomyolysis leading to acute kidney tubular necrosis. Target urine output for these patients should be at least 1 mL/kg/h [17]. The prevention of myoglobin precipitation in the renal tubules of these patients may necessitate the alkalinization of urine with sodium bicarbonate. With the development of rhabdomyolysis, electrolyte abnormalities, such as hyperkalemia, can develop, necessitating frequent monitoring of serum electrolytes and creatinine kinase until creatinine kinase levels are below 5,000 U/L [17].

Inhalation Injury

Inhalation injury remains one of the most important contributors to mortality in the burn population and is more common in children compared to adults. Inhalation injury is apparent in 20–30 % of all major burns and accounts for a 25–50 % increase in burn-associated mortality when patients require greater than 1 week of ventilator support. Anatomic differences between the airway in children compared to adults accounts for a disproportionate increase in the amount of tracheal resistance in children following inhalation injury [18]. Inhalation injury increases the mortality in children to approximately 40 % compared to burns in which the airway is not injured. The inhalation of toxic chemicals or smoke causes lower airway edema and irritation, resulting in the development of pneumonitis [19]. Burn inhalation injury results in the release of large amounts of inflammatory mediators such as neutrophils and cytotoxic substances. There is an increase in blood flow to the airway following inhalation injury, which results in bronchial micro-vascular permeability. The resultant sloughing of bronchial epithelium and increased lung permeability cause generation of free oxygen radicals, disrupting pulmonary epithelial integrity and leading to accumulation of protein-rich plasma in the lung. The presence of exudate subsequently leads to loss of surfactant, bronchospasm, obstruction, and even ulceration or necrosis of the airway [20]. Mortality from inhalation injury is increased to almost 60 % when combined with pneumonia in adults [21].

Inhalation injury is primarily diagnosed on the basis of direct bronchoscopic visualization and less often with arterial carboxyhemoglobin levels. In the emergency department, a laryngoscope can be used in place of a bronchoscope

for direct visualization of the upper airway. Clinical characteristics and physical examination findings such as facial burns, carbonaceous sputum, hyperemia of the airway, wheezing, and rales are used to diagnose smoke inhalation injury. Additionally, reports of entrapment within a closed space are important indicators of inhalation injury [22]. Airway compromise, which may take up to 48 h to present, can be anticipated with findings of dry or erythematous appearing mucosa or blisters in the oropharynx.

Once inhalation injury is suspected, patients should be placed on 100 % oxygen and immediately assessed to determine need for tracheal intubation and mechanical ventilation. Indications for tracheal intubation include, but are not limited to, upper airway obstruction, inability to clear secretions, hypoxemia despite oxygen administration, obtundation, muscle fatigue, and hypoventilation [5]. The presence of inhalation injury in children causes a decrease in lung compliance and increased work of breathing [23]. The goal of ventilation is to minimize the incidence of barotrauma, which can be accomplished by limiting plateau airway pressures to 35 cm H_2O or less and tidal volumes to 6 mL/kg of predicted weight. Permissive hypercapnea may be tolerated, with carbon dioxide levels allowed to rise as long as pH levels remain greater than 7.25. Hyperoxic lung injury should also be avoided by using low concentrations of supplemental oxygen. High-frequency percussive ventilation has been shown to be of greater benefit in maintaining these parameters in the pediatric population than conventional mechanical ventilation [5, 23]. Aerosolized heparin/N-acetylcystiene therapy has also been shown to reduce mortality in pediatric burn patients with inhalation injury by breaking down thick mucus secretions [24]. Bronchodilators, chest physiotherapy, and frequent suctioning should also be used to remove secretions.

Escharotomies and Fasciotomies

Deep superficial thickness and full thickness circumferential burns of the extremities, chest, and abdomen can result in an eschar formation with mechanical properties similar to leather, leading to loss of anatomic compliance. When the chest or abdomen is involved, this limitation in skin expansion can result in respiratory or hemodynamic compromise. Fluid resuscitation of the burn patient leads to trans-capillary efflux of fluid into the extracellular space. Over time, the noncompliant nature of eschar impedes venous outflow and arterial inflow and thus creates an increase in the pressure within the compartment (extremity, chest, or abdomen). The presence of a peripheral compartment syndrome can be identified by decreased or absent pulse oximetry (<90–95 %) or decreased Doppler probe signals, which reflect arterial flow in digital arteries. Another indicator of vascular compromise is the presence of pallor, pulselessness, pain, parasthesia, and paralysis. In addition, compartment tissue pressures can be measured by placing an 18 gauge needle, connected to an arterial pressure transducer, beneath the eschar and into the subcutaneous or sub-fascial space. Tissue pressures greater than 40 mmHg indicate the need for a releasing procedure to be performed, while pressures between 25 and 40 mmHg should warrant consideration of the same [15]. If these findings are present, decompressive escharotomies or fasciotomies are justified and can be performed at the bedside emergently with a scalpel or cautery [5]. The skin-releasing incision must be longitudinal through the skin and should extend down to the fat of the eschar to adequately restore blood flow. It should also be fashioned to avoid neurovascular structures and can be repeated on the opposing side if adequate flow does not result. Delay in treatment can result in tissue ischemia and necrosis, infection, muscle contracture, and eventual amputation.

Wound Care

Treatment of the burn wound is dependent on burn size and depth. Initial management includes proper analgesia, administration of tetanus booster and immune globulin, and debridement via thorough cleaning with soap and water [5]. In addition to removing necrotic tissue and blisters, cleaning the wound allows further assessment of the wound's depth and involved surface area [25]. Once adequately debrided, the wound should be dressed with a covering that will protect the damaged epidermis, minimize bacterial and fungal colonization, and serve as a splint to assist in the maintenance of functional positioning. The dressing should be comfortable and occlusive, minimizing heat loss [6]. Dressings should be changed twice daily, and the use of available topical agents should be based on wound location, depth, and presence of eschar. Wound cultures should be obtained initially to determine a baseline and then repeated weekly thereafter to ensure early detection of wound infections [25].

Topical Antimicrobial Agents

Prevention of wound infection is paramount for optimal healing and prevention of sepsis. Topical antimicrobial agents can be directly applied to wounds as a salve or poured onto dressings and applied as a soak. The use of each is determined by the severity of the burn and location of the wound. Salves require regular dressing changes, while soaks can cause maceration of the underlying skin. Topical agents that are commonly used in salve form on burn patients include ointments such as bacitracin, neomycin, polymyxin B, and mupirocin; creams such as 1 % silver sulfadiazine (silvadene) and 10 % mafenide acetate (sulfamylon); and antifungals such as nystatin. Topical agents applied as a soak include 0.5 % silver nitrate solution (available as a

commercial dressing), 0.025 % sodium hypochlorite (Dakin's solution), 0.25 % acetic acid, and 5 % mafenide acetate [6, 25].

The choice of topical antimicrobial agent is dictated by the characteristics of the wound, the location, and the speciation of infectious agent. First degree burns generally do not require dressing, as there is minimal loss of barrier function and lower risk of infection. Topical salves and oral pain medicines are sufficient for treatment of these injuries. Second degree burns require topical antibiotics and dressings with gauze and elastic wrap. A thin layer of bacitracin ointment impregnated into a temporary biologic membrane and covered with kerlix gauze is an effective treatment for these wounds. Third degree burns are treated with silver sulfadiazine cream and covered with bulky dressing. This dressing can easily be managed by the patient, is relatively painless, and does not produce electrolyte or acid/base abnormalities.

Sodium hypochlorite (Dakin's solution) is a broad-spectrum agent effective against gram negative and gram positive agents, in addition to being bactericidal for *Pseudomonas aeruginosa and Staphlococcus aureus*. Sodium hypochlorite is very effective as a cleansing agent, especially in the presence of necrotic tissue, and can often be used in combination with other topical agents. Silver sulfadiazine has broad spectrum coverage against gram positive and gram negative bacteria and has some antifungal properties. Penetration of the eschar by silver sulfadiazine is poor, however, and transient leukopenia (which will resolve without requiring treatment) may result. Silver nitrate (0.5 %) is a non-toxic solution that is bacteriostatic and has activity against Escherichia coli, *S. aureus*, and *P. aeruginosa*. Silver nitrate aqueous solution is also very effective for topical bacterial control. It has a broad spectrum of coverage; however, it is most efficacious in a wound which is clean and debrided of necrotic tissue. The main disadvantages of silver nitrate are limited penetration of eschar and alterations in serum electrolytes. Mafenide acetate is a carbonic anhydrase inhibitor that easily penetrates eschar and is effective against resistant *Pseudomonas* and *Enterococcus* species. It is, however, painful to apply and can lead to metabolic acidosis when used on large burns [6, 25]. In a wound with a large eschar, the microbial agent of choice would be mafenide acetate. This agent has good penetration of eschar and is effective against a broad range of microorganisms, including *Pseudomonas and Clostridium*.

Burn Excision and Closure Techniques

The burn wound is a significant source of inflammatory cytokines that drive the hypermetabolic response, leading to significant morbidity and mortality following a severe burn injury. Early excision and grafting of severe deep partial thickness and full thickness burns minimizes release of cytokines and progression of this response. Early surgical intervention is associated with decreased blood loss, wound infection, and length of hospital stay. Burns excised more than 48 h after injury have been associated with increased incidence of wound infections (bacterial and fungal) and sepsis. At our institution, the burn wound is generally excised to the level of viable tissue within 24 h of admission. This often involves total or near total tangential and/or fascial excision. Split-thickness autografts are taken with an electric or air dermatome and immediately applied to the burn wound site to re-establish the skin barrier. For massive burns, the autograft is then meshed 4:1 and covered with meshed 2:1 cadaveric allograft. Donor sites are covered with a sterile ointment dressing, and graft sites are directly covered with fine mesh moistened gauze or petroleum-based gauze product to prevent graft dessication. A second outer dressing is typically applied and the entire dressing secured using roller gauze or mild compression to allow graft adherence within 48–72 h. Further autografting is performed after donor sites have healed, with patients returning to the operating room every 5–10 days as needed, to ensure adequate coverage. The 4:1 autograft typically heals within 21 days, and the allografted cadaver skin then falls off. Hands are generally covered with sheet graft. The face and neck are treated with a mixture of polymyxin B and bacitracin ointments and then covered with sheet graft once the eschar has separated [26].

Wound Closure Alternatives

A number of wound closure alternatives can provide an adequate barrier against bacterial infection, wound desiccation, and evaporative heat loss. The current standard treatment for burn wounds is autografting with sheet graft in smaller burns and expanded autografts in conjunction with cadaveric skin for massive burns. When donor site availability is limited, cultured epithelial autograft (CEA) can be used. Keratinocytes are harvested from the patient's donor skin and cultured to produce a 6–8 epidermal cell thick product in approximately 2–3 weeks. These cultured cells can be applied directly to the wound bed and secured in place with staples. This process is costly, and the graft does not provide a long-term durable cover [27]. Temporary wound coverage should be attained with synthetic and biologic dressings until autograft skin is available. Biologic dressings used in burn wound management include cadaver or living donor allograft (homograft), heterograft usually from pig skin (xenograft), and amniotic membranes. These formulations usually develop fibrin bonds and show evidence of revascularization within 24–48 h, with the exception of amniotic membrane, which does not become engrafted or vascularized. Synthetic dressings include Biobrane (most commonly used) and Transcyte. Biobrane is a bilaminate membrane with a collagen-based dermal analogue that conforms well to body contours and allows freedom of motion. It is used to cover partial-thickness burns and

for short-term coverage of excised wounds. Transcyte is a skin substitute that uses biobrane as a carrier, seeded with neonatal fibroblasts that secrete matrix components such as collagen. The dermal replacement Integra is a bovine collagen/chondroitin-6-sulfate that allows fibrovascular in-growth from native fibroblasts. This in-growth allows formation of a neodermis within 2–3 weeks. Integra use allows the epidermal autograft taken from donor sites to be ultra-thin (0.006–0.008 in.), which leads to better staging for performing procedures, decreasing overall hospital stay. Alloderm, an acellular human cadaver allograft dermis, has also been used as a dermal replacement agent. It is placed on the burn wound with a thin split-thickness autograft overlay. Because it is acellular, alloderm is non-immunogenic. The advent of newer products has led to a decline in its use in recent years [27].

Nutritional Requirements After Burn Injury

Severe burn injury increases the metabolic demands of the body, leading to accelerated catabolism, hyperdynamic cardiac output, a negative nitrogen balance, and the loss of lean body mass [28]. This hypermetabolic state, which also causes an increase in glycogen catabolism and oxygen consumption in the liver and muscle, persists for up to 12 months post injury. Futile substrate recycling increases the demand for amino acids to meet the increased metabolic rate and protein catabolism. Patients become prone to infection and sepsis and develop multiorgan failure, potentially leading to mortality [29]. Nutritional supplementation is required to prevent continued malnutrition and severe weight loss. In third degree burns, the development of infection can be minimized through the early excision and immediate closure of the burn wound using a widely meshed autograft or biosynthetic skin substitute, in conjunction with adequate nutritional support [30].

Severe burn injuries cause gut mucosal atrophy secondary to the development of mucosal edema, intestinal dysfunction, energy deficiency, and increased gut permeability. Enteral nutrition should be provided as soon as it is clinically appropriate but ideally within the first 24–48 h. Early enteral support reduces gut atrophy, improves the immune response, attenuates the hypermetabolic response, and decreases mortality [31–33]. Daily caloric requirements can be estimated by multiplying the basal energy expenditure by two in patients with greater than 40 % TBSA burns. Alternatively, 25 kcal/kg/day plus 40 kcal per percent TBSA burned per day can be used as adequate estimation of caloric needs [6]. Continuous enteral or parenteral nutritional support with delivery of 1,800 kcal (7.56 mJ)/m^2 per day plus 2,200 kcal per m^2 of TBSA per day will maintain bodyweight in pediatric burn patients [30]. Nutritional supplementation at this level is necessary to support a metabolic rate of 1.4 times the resting energy expenditure. In pediatric patients, this can be estimated by indirect calorimetry on the basis of oxygen consumption and carbon dioxide production, and is adequate to maintain total body weight [30]. For patients tolerating oral intake, low-fat, high-carbohydrate diets are associated with shorter durations of hospital stay. Supplementation with essential amino acids such as glutamine and arginine improves wound healing, increases hormonal expression, modulates cell-mediated immunity, maintains gut integrity, and reduces overall mortality [34]. Oral intake is often limited in small children, due to the pain and anxiety associated with an acute burn injury. Enteral nutrition in children with limited oral intake can be achieved with infusion of formula through feeding tubes. Most infants require large fluid volumes and should not receive concentrated formula. Overfeeding is an important concern in pediatric burn patients. Fatty infiltration of the liver is seen in these patients with overfeeding, both with enteral and parenteral supplementation. Excess calories cause fat accumulation without positively affecting lean mass and lead to complications of hyperglycemia and increased rates of infections [35, 36].

Complications

Burn shock has historically been an important cause of mortality following severe burn injury. Recent improvements in the multidisciplinary management and timely resuscitation of patients have resulted in a reduction of burn shock-related mortality. As a result, complications associated with wound infection have become increasingly more significant as a cause of morbidity and mortality. Patients with severe burns are immune suppressed with increased susceptibility to infection during wound healing [37]. Necrotic tissue has no resistance to infection and often provides an ideal growth media for infectious agents. Surgical excision of dead tissue, often to the fascial level, must be undertaken to prevent infection. Complete excision of necrotic tissue and the use of topical antimicrobials is currently the standard of care. The use of prophylactic intravenous antibiotics is discouraged – once infection is identified, however, intravenous antibiotics are rapidly instituted. Infection of a burn wound can often be difficult to identify secondary to the existing erythema, tenderness, and edema associated with burn injury. Fever and purulent drainage, however, are indicative of infection and necessitate the initiation of broad spectrum antibiotics. Antibiotics should be started immediately and the wound excised and grafted with a temporary biological dressing, as sepsis can proceed rapidly [6, 19]. Patients who present with inhalation injury are at increased risk for development of pneumonia (especially following prolonged intubation), urinary tract infections, and catheter-related infections (secondary to prolonged hospitalization). Less severe

complications associated with burn injuries include contractures and hypertrophic scar formation. Contractures can be minimized by diligent wound care and physical therapy. Development of hypertrophic scars can also be minimized with physical therapy and pressure dressings; however, ethnic groups with large amount of pigmentation are prone to develop these scars. Most therapies are ineffective for treatment of hypertrophic scars and contractures occurring across joints, necessitating reconstructive surgical procedures.

Rehabilitation and Long Term Care

Maintenance of body mass index is requisite for optimal wound healing. This can be achieved with a structured aerobic and resistance exercise program, which can improve overall strength by approximately 50 % in addition to minimizing formation of contractures. In pediatric patients, a 12-week aerobic resistance exercise program improves lean body mass, power, and strength [30, 38]. Exercise also facilitates the maintenance of joint mobility, range of motion, and overall improvements in performing activities of daily living [39].

Children develop strong psychological and physical limitations from their burn injuries because social acceptance strategies and interactions are primarily developed during childhood. The presence of a disfiguring burn wound may inhibit their ability to confidently interact with peers during the early stages of social development. The multi-disciplinary approach to burn care, with the inclusion of psychiatrists and/or psychologists, is especially important in addressing the psychological and social needs of burned children.

Conclusion

Pediatric burn patients are a very special population with unique physiologic and psychologic needs. Accurate initial estimate of burn injury, adequate resuscitation, and timely surgical intervention are of paramount importance to ensure good outcomes. Advancements in fluid resuscitation, early surgical excision and grafting of the burn wound, infection control, and critical care have reduced morbidity and mortality in pediatric burn patients. In 1949 the expected mortality for a child with 49 % TBSA burn was 50 %. As a result of improved clinical care, it isn't until the TBSA burned in a child reaches 98 % that 50 % mortality is expected. Educational efforts are critical to the prevention of burn injuries. As the majority of severely burned patients continue to survive, emphasis on supporting the psychologic needs and addressing underlying pathophysiologic process leading to physical disfigurement (such as hypertrophic scar formation) will be critical in allowing these children to re-integrate into society and lead healthy, productive lives.

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Part IV

Cardiac Surgery and Critical Care

Bradley S. Marino

The Systemic Inflammatory Response to Cardiopulmonary Bypass: Pathophysiology and Treatment

21

Ronald A. Bronicki and Mark S. Bleiweis

Abstract

Exposure of the blood elements to the bioincompatible cardiopulmonary bypass circuit and cardiac and pulmonary reperfusion injury stimulate a systemic and regional inflammatory cascade, which culminates in tissue injury. Invariably, the inflammatory response to bypass affects post-operative management, potentially contributing to morbidity and mortality. Over the last 40 years, our understanding of the inflammatory response to bypass has increased dramatically. This understanding has modified practice and has favorably impacted patient care. In this review, we discuss the pro- and anti-inflammatory response to bypass; the pathophysiology of immune-mediated tissue injury, including the sequelae of reperfusion injury on organ function; and immunomodulatory therapies.

Keywords

Systemic inflammatory response • Compensatory anti-inflammatory response • Reperfusion injury • Cardiopulmonary bypass • Immunemodulatory therapies

Introduction

Since the first successful use of cardiopulmonary bypass (CPB) for intracardiac surgery (closure of an atrial septal defect) in 1953 by Dr. John Gibbon, innovations such as the creation of more biocompatible surfaces and miniaturization of circuits, as well as the increasing expertise of surgeons, anesthesiologists and perfusionists has transformed cardiac surgery and the use of CPB into a relatively routine procedure with favorable outcomes [1]. Despite these refinements, the attendant inflammatory response resulting from the use of CPB contributes to complications such as organ dysfunction, increased length of stay, and mortality.

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History

Our understanding of the inflammatory response to CPB began in earnest with the observation made by Craddock and colleagues in the 1970s that uremic patients undergoing hemodialysis developed hypoxia and neutropenia [2]. They subsequently demonstrated that autologous plasma incubated with dialyzer cellophane and injected into animals produced sudden leukopenia, hypoxia and a marked increase in pulmonary lymph effluent; histologic examination demonstrated pulmonary leukosequestration and edema; and the syndrome could be prevented by inactivation of complement. Subsequently, Kirklin and colleagues demonstrated significant complement activation in adults with the onset of CPB [3]. Two years later, Kirklin and colleagues found a positive relationship between complement activation and post-operative morbidity in adults and children undergoing cardiac surgery [4].

During the 1980s, additional pro-inflammatory mediators were discovered and inflammatory mediator assays became readily available, which led to a greater understanding of the immunologic response to CPB, as well as other diseases, such

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as septic shock, trauma and heart failure [5]. The understanding that infectious and non-infectious stimuli (including, CPB) can trigger an inflammatory response and an increasing appreciation of the effects that the inflammatory cascade has on organ function, led to the American College of Chest Physicians and the Society of Critical Care Medicine in 1992 to coin the term "Systemic Inflammatory Response Syndrome" (SIRS).

Pathophysiology of the CPB-Induced Inflammatory Response

With exposure of plasma proteases to the non-endothelial lining of the CPB circuit, the contact system and alternate pathway of complement are activated. The contact system, consisting of factors XII and XI, prekallikrein and high-molecular-weight kininogen (HK), is activated when factor XII and its cofactor HK come into contact with a foreign surface. Activated factor XII (XIIa) converts prekallikrein into kallikrein, which in turn converts HK into bradykinin. Factor XIIa also activates the intrinsic coagulation pathway. Vascular injury leads to increased tissue factor expression, activating the extrinsic coagulation pathway and further contributing to the coagulation cascade. Thrombin and plasmin, byproducts of the coagulation and fibrinolytic systems, kallikrein and XIIa activate the classical pathway of complement. Byproducts of the plasma proteases activate endothelial cells, platelets, leukocytes, macrophages and parenchymal cells leading to the production of cellular-derived inflammatory mediators, such as arachidonic acid metabolites, including prostaglandins and leukotrienes; platelet-activating factors; histamine; lysosomal enzymes; reactive oxygen species; nitric oxide; and cytokines, including interleukins, interferons and tumor necrosis factor-α (TNF-α).

Another factor in the pathophysiology of the inflammatory response to CPB is ischemia-reperfusion injury. Myocardial and pulmonary ischemia-reperfusion injury is in large part an inflammatory phenomenon. Following a period of ischemia, reperfusion stimulates the release of additional pro-inflammatory mediators, particularly reactive oxygen species and cytokines, by parenchymal, endothelial, platelet and inflammatory cells, contributing to elevated serum levels of inflammatory mediators [6]. At the conclusion of CPB, the formation of heparin-protamine complexes further stimulates the classical pathway of complement. Virtually every inflammatory pathway and nucleated cell is activated and capable of contributing to the inflammatory cascade. The inflammatory response may be systemic in nature, as with activation of plasma proteases by the bioincompatible bypass surface, or primarily parenchymal in nature, as occurs with pulmonary and myocardial reperfusion injury.

Inflammatory mediators possess a wide range of biologic properties, with the hallmark of the systemic inflammatory response being fever, vasodilation, an increase in microvascular permeability and the formation of interstitial edema, and a significant increase in total body oxygen consumption [7]. Chemoattractants (primarily activated components of complement C5 and C3, cytokines and leukotrienes) guide the migration of bloodborne inflammatory cells towards the source of inflammation. The inflammatory cascade culminates with activation of leukocytes, platelets and endothelial cells by inflammatory mediators (most notably cytokines) and the expression of complementary cell-surface adhesion molecules, such as integrins and selectins, which enable platelets and leukocyte to roll along and adhere to the endothelium. Activation of leukocytes results in degranulation and secretion of lysosomal enzymes and an oxidative burst. The release of reactive oxygen species and tissue-destructive proteases cause endothelial injury or detachment, resulting in increased vascular permeability, and parenchymal injury. Inflammatory mediators (primarily histamine, bradykinin, leukotrienes and cytokines) induce endothelial cell contraction, creating intercellular gaps, thereby contributing to increases in vascular permeability. Cell death results from coagulation necrosis and inflammatory mediator-induced apoptosis. Central to the pathophysiology of reperfusion injury is endothelial damage, resulting in impairment of the nitric-oxide-cGMP signaling cascade and endothelial-dependent vasodilation [8]. An imbalance between vasodilators and constrictors, microthrombi and leukocyte plugging further compromise reperfusion.

Several pre- and or co-existing factors stimulate inflammation, contributing to the inflammatory response. Shock states stimulate inflammatory responses and genetic factors are an important determinant of the inflammatory response to a variety of stimuli [9, 10]. In hypoxic conditions, hypoxia-inducible factor translocates to the nucleus, where it induces transcription of numerous inflammatory genes [11]. Heart failure is characterized by sustained immune activation, reflected in increased circulating levels of inflammatory cytokines and enhanced expression of various inflammatory mediators within the failing myocardium (e.g., adhesion molecules, cytokines and nitric oxide) [12]. Mechanical cell stress as with a pressure or volume load resulting from structural heart disease stimulates an inflammatory response [13]. Inflammatory mediators are not only markers of immune activation but contribute to the pathophysiological process of heart failure by stimulating myocyte apoptosis, myocyte hypertrophy, extracellular matrix alterations and contractile dysfunction [14].

Compensatory Anti-inflammatory Response Syndrome

With initiation of the pro-inflammatory cascade, a compensatory anti-inflammatory response ensues, which serves to limit the inflammatory response and extent of tissue

injury [15]. The discovery of anti-inflammatory mediators followed on the heels of an increasing appreciation of the pro-inflammatory response and culminated with the coining of the term "Compensatory Anti-inflammatory Response Syndrome" (CARS) in 1996 [16]. The production of anti-inflammatory mediators, the most prominent being interleukin-10, is in part stimulated by the preceding pro-inflammatory response, creating an autoregulatory feedback loop. The CARS is characterized by a decrease in immunologic competence, resulting from multiple mechanisms, including apoptosis of immune effectors cells and a decrease in the expression of major-histocompatibility-complex class II molecules (e.g., HLA-DR).

An inadequate CARS allows for an excessive pro-inflammatory response, which is exemplified in patients with fulminant meningococcemia. The importance of this compensatory anti-inflammatory response has also been demonstrated in studies of cerebral, pulmonary and myocardial ischemia-reperfusion injury, where the parenchyma-derived anti-inflammatory response serves to limit the extent of reperfusion injury [17–21]. If however the CARS is excessive in terms of magnitude or duration, a state of immune suppression develops (or immune paralysis), that may lead to a failure to eradicate an inciting infection; reactivation of a latent viral infection; or to the development of a secondary nosocomial infection [22]. Several studies have demonstrated worse outcomes in trauma, sepsis and following cardiac surgery and CPB in those patients with evidence of prolonged immune suppression [23–25]. For example, Allen and colleagues studied 82 infants and children undergoing cardiac surgery and CPB and found reduced monocyte expression of HLA-DR in all patients post-operatively compared with pre-operative levels [25]. A multivariate analysis identified HLA-DR expression as an independent predictor of secondary sepsis after controlling for other variables. And as is the case with the pro-inflammatory response, genetic factors are an important determinant of the compensatory anti-inflammatory response [26, 27].

End Organ Injury and the Inflammatory Response to CPB

Cerebral Injury

Circulating inflammatory mediators bind to receptors on cerebral vascular and vascular-associated cells, producing an increase in the permeability of the blood-brain-barrier and cerebral edema while inducing the central synthesis of intermediate molecules such as prostaglandins and cytokines, which serve as ligands for specific receptors within parenchymal elements of the brain [28–30]. The binding of these intermediate ligands to nuclei within the brain modulate several central functions, such as thermoregulation, behavior (e.g., anorexia, cachexia and lethargy), the autonomic nervous system and the hypothalamic-pituitary adrenal (HPA) axis [31].

Based on animal and clinical studies it does not appear that the CPB-induced systemic inflammatory response causes long-term neurocognitive dysfunction [32–34]. In patients requiring circulatory arrest, the primary mechanism of immune-mediated cerebral injury results from ischemia-reperfusion injury [35, 36]. Re-establishing cerebral blood flow leads to a local inflammatory cascade, with the production of proinflammatory mediators, primarily cytokines and reactive oxygen species, by leukocytes, platelets, endothelial cells and resident brain cells, such as microglia, neurons and astrocytes. The inflammatory cascade culminates with the extravasation of activated leukocytes and cerebral injury.

Reperfusion injury results in impaired endothelial-dependent vasodilation and in some patients impaired cerebral pressure autoregulation (CPA). When this occurs, cerebral blood flow is no longer coupled to cerebral metabolism and a pressure-passive circulation develops, where cerebral blood flow changes in parallel with changes in systemic pressure. Studies in animals, children and adults have demonstrated disturbed CPA following circulatory arrest [37–41].

Pulmonary Injury

The systemic inflammatory response and pulmonary reperfusion injury impair respiratory function. The importance of reperfusion injury has been demonstrated in several animal and clinical studies [42–45]. Damage to the alveolar-endothelial barrier leads to permeability pulmonary edema. Interstitial and alveolar edema decreases lung compliance. Impaired surfactant production resulting from injury to type II alveolar pneumocytes and the inactivation of surfactant by extravasated plasma proteins further decrease lung compliance and functional residual capacity, leading to ventilation-perfusion mismatch and hypoxemia [46–48]. Pre-existing lung disease, prolong duration of CPB and ischemia, and pulmonary venous hypertension contribute to lung injury.

The systemic inflammatory response and pulmonary reperfusion injury also cause pulmonary endothelial dysfunction and increases in pulmonary vascular resistance. As with alveolar injury, several animal studies have demonstrated that reperfusion injury plays a major role in the development of pulmonary vascular dysfunction [49, 50]. Shafique et al. demonstrated that sheep undergoing CPB with pulmonary arterial perfusion maintained vascular function whereas those animals undergoing total CPB experienced significant alterations in endothelial-dependent vascular responses.

The primary mechanism responsible for pulmonary vascular dysfunction is impairment of the nitric oxide-cGMP signaling cascade. Wessel and colleagues demonstrated in

children following cardiac surgery and CPB that the pulmonary vascular response to nitric oxide was preserved, whereas receptor-mediated vasodilation was markedly diminished [51]. Subsequent studies have since demonstrated that following CPB, plasma levels of the nitric oxide precursor L-arginine are reduced and its supplementation partially restores nitric oxide production [52–54] additionally, the release of systemic and pulmonary derived inflammatory mediators alters the balance between vasoconstrictors and vasodilators, contributing to increases in pulmonary vascular resistance [55].

Cardiovascular Injury

The inflammatory response to CPB and the reperfusion injury that follows cardioplegic arrest leads to myocardial injury and impaired function. Inflammatory mediators, primarily cytokines produced by cardiomyocytes and interstitial cardiac leukocytes, exert a direct effect on the cardiomyocyte, impairing systolic and diastolic ventricular function [56, 57]. Vaso- and cytogenic edema decrease ventricular compliance, contributing to impaired diastolic function [58, 59]. The major insult to the myocardium occurs with reperfusion following cardioplegic arrest. While calcium overload and myocyte hypercontracture contribute to reperfusion injury, the primary mechanism responsible for myocardial injury is reperfusion-induced inflammation [60, 61]. Cell death results from tissue necrosis and cytokine-mediated apoptosis. Because myocardial apoptosis is a part of normal fetal and postnatal maturation, the neonatal myocardium may have an increased vulnerability or susceptibility to apoptosis-related processes following surgery, contributing to post-operative ventricular dysfunction [62, 63]. Endothelial dysfunction contributes to the pathophysiological process. The decrease in nitric oxide production leads to impaired coronary vasodilatory reserve [64, 65] and because nitric oxide modulates leukocyte-endothelial cell and platelet-endothelial cell interaction, a decrease in nitric oxide bioavailability contributes to the pro-coagulant and pro-inflammatory state and microvascular obstruction as a result of thrombosis and leukocyte accumulation [66, 67].

The inflammatory response to CPB response may also affect systemic vascular function. Excessive vasodilation of venous capacitance and arterial resistance vessels leads to inadequate systemic venous return and systemic hypotension. Systemic vascular tone is regulated by neurohormonal systems and endothelial function, both of which may be affected by the inflammatory response [68]. Inflammatory mediators such as histamine, bradykinin and nitric oxide may produce a state of vasodilatory shock. While a systemic inflammatory response invariably occurs to CPB, why a minority of patients develop vasoplegia remains unclear [69–71]. The systemic inflammatory response may also affect vascular function by interfering with the HPA axis, resulting in decreased cortisol production, a relative adrenal insufficiency and, because cortisol is required for vascular tone, vasodilatory shock [72–74]. Studies have demonstrated that cytokines such as TNF-α affect various levels of the HPA axis, suppressing cortisol production [75, 76].

Renal Injury

The role of immune-mediated renal injury following CPB has not been extensively studied. Animal models have demonstrated that CPB-induced inflammation results in glomerular and renal tubular damage that is associated with endothelial cell injury and activation and leukocyte sequestration, as well as reduced glomerular filtration rates and creatinine clearance [77, 78]. Animal models of renal ischemia-reperfusion injury have clearly demonstrated the role of inflammation in producing tubular injury and dysfunction, findings much more dramatic than those reported for CPB-induced inflammation alone [79].

Mesenteric Injury

Several studies in adults and children have demonstrated that the CPB-induced inflammatory response increases intestinal permeability [80, 81].

Several studies have also demonstrated an inverse relationship between indices of mesenteric perfusion and increases in intestinal permeability during CPB, indicating that despite adequate pump flow mesenteric ischemia contributes to intestinal injury [82–84]. Non-pulsatile flow stimulates the renin-angiotensin system, leading to increases in mesenteric vascular resistance and contributing to mesenteric ischemia [85]. Ischemia-reperfusion injury following circulatory arrest contributes to tissue injury [86]. The systemic inflammatory response and reperfusion injury also cause mesenteric endothelial dysfunction and impaired endothelial-dependent vasoreactivity [87, 88].

Inflammation and ischemia-related injury compromise the integrity of the mucosa, resulting in bacterial translocation and further stimulation of the inflammatory cascade. Studies in infants, children and adults have demonstrated that bacterial translocation during cardiac surgery is common, regardless of whether circulatory arrest is used [81, 82, 89]. Lequier and colleagues evaluated the clinical relevance of endotoxemia in children with severe congenital heart disease prior to and following surgery (n = 30) [89]. Ninety-six percent of patients had evidence of endotoxemia (lipopolysaccharide [LPS] and LPS-binding protein) during the study period. Fifty percent of patients met prospectively defined criteria of severe hemodynamic disturbance during their

postoperative course. These patients had significantly higher preoperative indicators of endotoxemia compared to patients with less severely disturbed hemodynamics. Mortality was 25 % in patients with preoperative endotoxemia compared with no mortality in patients who were not endotoxemic prior to surgery.

Immunomodulatory Therapies

Numerous immunomodulatory strategies have been evaluated in animals and clinical trials [90]. The vast majority of pediatric centers in North America and the United Kingdom have incorporated the use of glucocorticoids (GC), modified ultrafiltration (MUF) and heparin-coated circuits into practice [91–93].

Glucocorticoids

Glucocorticoids are highly effective at suppressing virtually every pro-inflammatory pathway and augmenting the compensatory anti-inflammatory response. Whether or not GCs improve the post-operative course and are safe remains controversial [94–96]. Important factors to consider when evaluating the role of GCs in ameliorating the CPB-induced inflammatory response are the dose and timing of administration. The primary mechanism by which GCs modulate inflammation is by modifying gene expression; thus the time allotted for priming of the immune system prior to its exposure to stimuli (i.e., blood-CPB interaction and reperfusion injury) is an important determinant of the immune-suppressive effects [97–100].

There have been six small prospective randomized controlled trials of GCs in children undergoing cardiac surgery. Bronicki and colleagues randomized children to dexamethasone (1 mg/kg) or placebo (n = 29) following induction of anesthesia [101]. Following surgery patients randomized to GC had significantly less fever, required less supplemental fluid, had greater preservation of renal function and less impairment of oxygenation, and experienced a significantly shortened duration of mechanical ventilation and length of stay in the intensive care unit. This trial was followed by a dose-response study by Schroeder and colleagues who randomized children (n = 29) to methylprednisolone (30 mg/kg) 4 h prior to CPB and in bypass prime or to a single dose in the bypass prime [102]. Those patients who received two doses of GCs had significantly less fever, required less fluid, had a significantly reduced oxygen extraction ratio and experienced a trend toward reduced length of stay in the intensive care unit ($p = 0.07$).

Checchia and colleagues (n = 28) and Malagon and colleagues (n = 140) demonstrated reduced myocardial injury based on serum troponin levels following surgery in those children randomized to GCs following induction of anesthesia [103, 104]. Malagon et al. also evaluated post-operative clinical parameters and found those patients randomized to treatment had significantly greater fluid balance and a trend toward reduced serum lactate levels following surgery. Two prospective studies failed to demonstrate benefit from the use of GCs however they limited enrollment to older children. Lindberg et al. randomized children to dexamethasone (1 mg/kg) or placebo after induction of anesthesia and did not find an improved post-operative course in those receiving therapy [105]. Of note, patients <10 kg were ineligible for enrollment, excluding the most complex lesions. Varan et al. conducted a dose-response study in which patients were randomized to receive high v. low-dose methylprednisolone (30 mg/kg v. 2 mg/kg, respectively; n = 30) prior to CPB and did not demonstrate benefit between groups [106].

Modified Ultrafiltration

Modified ultrafiltration is used in the vast majority of pediatric cardiac centers [93]. Ultrafiltration removes water, reverses hemodilution and eliminates low-molecular-weight substances, including inflammatory mediators [107]; these devices may be used during CPB (i.e., conventional ultrafiltration, CUF) or once CPB is completed (i.e., MUF), with the composition of filtrates being identical and the assertion that a greater amount of fluid and therefore solute may be removed following CPB than can be removed with CUF alone. While some studies have shown a significant beneficial effect of MUF on the post-operative course, others have failed to do so [108–110].

Heparin-Coated Circuits

Heparinization of the contact surface of the circuit was initially done to minimize thrombus formation; subsequently, heparin-bonded circuits have been shown to modify the inflammatory response to bypass, decreasing cytokine release as well as inhibiting the contact system and complement activation. Two small prospective randomized studies in children demonstrated significant reductions in serum inflammatory mediators levels and modest improvements in respiratory function and coagulation [111, 112].

Conclusion

Significant advances have been made in our understanding and treatment of the inflammatory response to CPB. Invariably to a varying extent, the CPB-induced inflammatory response affects the recovery of children following cardiac surgery. Further insight into the pathophysiology of the pro-inflammatory response, in particular cerebral

and myocardial reperfusion injury, and the CARS will lead to the implementation of additional therapies and contribute to improved outcomes.

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Myocardial Protection

22

Aaron W. Eckhauser and Thomas L. Spray

Abstract

The concept of myocardial protection in congenital heart surgery has dramatically evolved over the last two decades. Pediatric clinical practice has largely been extrapolated from experiences with adult myocardial protection. These practice patterns did not account for the inherent anatomic and physiologic differences between adult and immature myocardium that can make immature myocardium more (reduced free radical scavenging, increased calcium sensitivity) or less (preference to glucose, high glycogen stores and low 5′ nucleotidase activity) susceptible to ischemia. Neonatal hearts are also equally or more susceptible to global ischemia when exposed to chronic volume and pressure overloading and chronic hypoxia. This chapter will discuss the physiology of neonatal and immature myocardium and summarize the most current research done in pediatric myocardial protection over the last 20 years regarding different cardioplegia solutions and additives, temperature and cardiopulmonary bypass strategy and reperfusion techniques.

Keywords

Myocardial protection • Cardiopulmonary bypass • Cardioplegia • Congenital heart surgery • Perfusion technique

Introduction

The concept of myocardial protection in congenital heart surgery has dramatically evolved over the last two decades. A significant amount of clinical practice has been extrapolated from experiences with adult myocardial protection. These practice patterns did not account for the inherent physiologic differences between neonatal and mature myocardium, differences in loading conditions and the effects of chronic cyanosis found in congenital cardiac disease. The importance of pediatric myocardial protection gained attention in 1984 when Bull et al. [1] published their data studying the effects of cardioplegia on myocardial injury, highlighting the need for further research and improved methods of myocardial protection. This chapter will discuss the physiology of neonatal and immature myocardium and summarize research done in pediatric myocardial protection over the last 20 years.

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Physiology of Immature Myocardium

Structurally, immature myocardium (IM) has a higher water and protein content compared to adult myocardium. As a result, the denser immature myocardium is less compliant and functions in a much narrower range along the Frank-Starling curve. Immature myocardium has a lower rate of maximum tension development, reduced inotropic

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reserve and a decreased sensitivity to catecholamines due to decreased coupling of the myocardial β-adrenergic receptor to adenylate cyclase. Immature myocardium also has a greater negative inotropic response to anesthetic induction [2, 3]. Pathologically, immature myocardium is not only very different from mature myocardium but exhibits a high degree of variability when compared to other neonatal myocardial cells. Differences in neonatal cellular maturity are affected by age and underlying cardiac anomalies [4].

Immature myocardium also differs from adult myocardium by its substrate use for energy metabolism. The adult myocardium uses multiple substrates for energy production including lipids, carbohydrates and amino acids with up to 90 % of ATP production resulting from the oxidation of fatty acids [5, 6]. Immature myocardium is unable to readily oxidize fatty acids and relies more heavily on anaerobic metabolism using glucose obtained from glycogenolysis as its main energy source. As such, immature myocardial cells have abundant glycogen stores which occupy a higher proportion of cellular space than in adult myocardial cells [3, 5, 7].

Immature myocardium more rapidly utilizes glycogen which results in a swift accumulation of lactate. Elevated levels of lactate have been shown to inhibit glycolysis leading to an incomplete use of glycogen and a more rapid depletion of endogenous ATP [8]. The ultimate effect of rapid ATP depletion is ischemic contracture due to inhibition of the sarcoplasmic reticulum's ability to uptake calcium, leaving contractile proteins in their active state.

Immature myocardium is also much more reliant on extracellular calcium concentrations for optimal function compared to the adult heart. The reason for this is multifactorial and includes an underdeveloped sarcoplasmic reticulum with reduced storage capacity for calcium and decreased calcium adenosine triphosphatase activity leading to a decreased ability to release and re-uptake calcium upon stimulation [3, 5, 6].

Immature myocardium has an underdeveloped antioxidant defense system including superoxide dismutase, catalase and glutathione reductase [5, 9]. This becomes relevant when the immature myocardium is unable to deal satisfactorily with the increased amount of circulating free radicals after cardiopulmonary bypass and ischemia and reperfusion. In addition, immature myocardium has decreased enzymatic activity of 5′ nucleotidase which converts adenosine monophosphate into its diffusible precursor adenosine. The ultimate effect of this deficient enzyme is that there is a larger stored pool of adenine which is thought to improve immature myocardial tolerance to ischemia [5, 10].

Even amongst children there are still significant age related differences in the myocardial response to hypoxia and reperfusion. Imura et al. demonstrated that children (age >1 year) show more resistance to reperfusion injury than infants (age <1 year). In addition, children with cyanosis had worse outcomes after heart surgery than acyanotic children. The difference between cyanotic and acyanotic myocardium was not reproduced in infants [11].

Table 22.1 Etiology of immature stress

Volume overload
Left-to-right shunt
ASD
VSD
CAVC
PDA
Aorticopulmonary connection
Truncus arteriosus
AP window
AV or SV insufficiency
Pressure overload
Right-sided obstruction
PS
TS
Left-sided obstruction
AS or MS
HLHS
Coarctation
Subaortic stenosis
Shones complex
Interrupted arch
Cyanosis
Decreased PBF
TOF
TA, TS
HRHS
PA/IVS
Critical PS
Ebsteins anomaly
Increased PBF
TGA
TAPVR
Truncus arteriosus

In summary, anatomic and physiologic differences between adult and immature myocardium can make immature myocardium more (reduced free radical scavenging, increased calcium sensitivity) or less (preference to glucose, high glycogen stores and low 5′ nucleotidase activity) susceptible to ischemia [5].

Physiologic Stresses Unique to Congenital Cardiac Disease

There is an abundance of literature stating that immature myocardium has an improved tolerance to ischemia. This axiom may exist in the unstressed immature heart, but more recent data shows that stressed neonatal hearts are equally or more susceptible to global ischemia compared to adult myocardium [3, 8, 12, 13]. These stressors include chronic volume and pressure overloading and chronic hypoxia (Table 22.1).

Table 22.2 Determinants of myocardial oxygen consumption

Intramyocardial tension
Ventricular pressure
Ventricular volume
Myocardial mass
Heart rate
Contractile state
Force-velocity relation
Maximal contraction velocity
Basal metabolism
Work
External work
Internal work

Many congenital cardiac abnormalities result in physiologic and anatomic shunts with a high *Q*p:*Q*s and subsequent volume overloading of the heart. Immature myocardium, which already physiologically functions at a high diastolic volume, has a limited reserve and the additional volume can rapidly lead to hypertrophy, dilation and increased myocardial oxygen requirements. Similarly, congenital lesions resulting in outflow obstruction or increased afterload can pressure overload the heart causing hypertrophy. Ventricular hypertrophy reduces diastolic compliance and increases myocardial oxygen consumption. In addition, hypertrophy affects regional blood flow causing subendocardial ischemia [3, 12, 13].

Chronic hypoxia, also very common among patients with congenital heart anomalies, results in the depletion of glycogen stores, ATP and Kreb's cycle intermediates. Coupled with acidosis from anaerobic metabolism, the hypoxic heart is more dysfunctional than the unstressed heart and is less responsive to catecholamines, more prone to rapid ATP depletion and exhibits a decreased recovery of systolic and diastolic function after ischemia and reperfusion [3, 6, 12–14].

Myocardial Protection Strategies

The underlying principles of pediatric myocardial protection, namely reducing metabolic activity and the safe arrest of the hearts contractile state, are very similar to those used in adults. Changing the metabolic activity of the heart can be accomplished most effectively by altering the heart rate, contractility and the amount of tension developed within the heart (Table 22.2) [6, 15]. The most effective clinical methods of decreasing MVO_2 are hypothermia, decompression and electromechanical arrest.

Oxygen consumption decreases by almost 50 % when the heart is cooled to 32 °C. At temperatures below 12 °C oxygen consumption falls below 1 % of normal [5]. Additionally, potassium induced electromechanical arrest can decrease myocardial oxygen consumption by 60 % in empty, beating hearts and up to 90 % in a fully ejecting heart at normothermia [6, 16, 17]. The immature myocardium is also very sensitive to distension and stretch injury. Adequate venting of the heart can help to protect against this injury and help to prevent the occurrence of complications such as "pump lung" [14].

Cardioplegia

Since Bull et al. first published their data advocating for better pediatric myocardial protection, literally hundreds of different cardioplegia solutions and strategies have been employed. The fact that so many different solutions exist confirms that no one solution is clearly superior. However, the basic tenants of cardioplegia should remain for all solutions, namely (1) the ability to produce immediate arrest, (2) hypothermia, (3) substrates, (4) appropriate pH, and (5) membrane stabilization (low Ca^{+2}, Mg^{+2}, steroids and free radical scavengers) [12, 13].

Crystalloid vs. Blood

Research performed as far back as the 1970s shows that blood cardioplegia is more efficacious than crystalloid. In studies of adults, Bruckberg et al. found that blood cardioplegia had greater oxygen content (oxygenated crystalloid cardioplegia contains only a fourth as much O_2 as blood cardioplegia), superior buffering capacity due to blood protein histidine groups, improved microvascular flow, free radical scavengers and less tissue edema compared to crystalloid [17, 18].

Durandy et al. outline several important studies showing the superiority of blood vs. crystalloid cardioplegia. A large, adult meta-analysis showed that blood cardioplegia significantly decreased low-cardiac output syndrome and creatinine kinase MB release compared to crystalloid cardioplegia [16, 19]. In their own studies, Allen et al. found that there was no difference between crystalloid and blood cardioplegia when used in normal neonatal hearts. However, they found that in stressed "hypoxic" neonatal hearts that blood cardioplegia protected the heart from further damage and actually facilitated repair during hypoxia and reperfusion compared to crystalloid [12, 13]. Allen et al. found that by using blood cardioplegia, the heart is arrested in an oxygenated environment which can help to resuscitate the injured myocardium with oxygen and nutrients.

In a study of stressed neonatal piglet hearts, Bolling et al. found that blood cardioplegia resulted in preserved systolic function, preload recruitable stroke work and increased diastolic compliance. In conclusion, they found similar results to Allen et al. that in non-stressed hearts there was no difference in type of cardioplegia, but in hypoxically stressed hearts blood cardioplegia provided optimal results [20].

Amark et al. studied the differences in blood vs. crystalloid cardioplegia in patients undergoing repair of atrioventricular septal defects and found that blood cardioplegia resulted in less lactic acidosis and better cardiac function coming off and

immediately post-bypass. These differences were felt to be significant during a time when the neonatal heart is most vulnerable [21]. Vittorini et al. found that certain isoforms of heat shock proteins, which are protective against myocardial cell damage and reperfusion injury, were upregulated in pediatric patients perfused with blood cardioplegia during aortic crossclamp [22].

Cold vs. Warm

Significant controversy also exists surrounding the optimal temperature of cardioplegia. In an extensive analysis of cardioplegia in adults, Mauney et al. report that cold blood cardioplegia causes a rightward shift in the oxyhemoglobin saturation curve, limiting the amount of oxygen available to the tissues. At temperatures of 20 °C only 50 % of total oxygen content is available to the tissues, dropping to 30 % at temperatures below 10 °C. In addition, hypothermia can lead to cardioplegia sludging, activation of cold agglutinins and formation of rouleaux (stacking of red blood cells) [17]. Conversely, normothermic induction of arrest was found to actively resuscitate deprived myocardium during the application of aortic cross-clamping [23]. Warm blood cardioplegia, especially a terminal "hot shot" infusion was found to mitigate the deleterious effects of reperfusion injury, namely intracellular calcium accumulation, edema and the inability to utilize delivered oxygen. In another extensive analysis of cardioplegia in adults, warm induction and cardioplegia were found to improve the hearts tolerance to the initial and subsequent periods of ischemia, prevent oxidative stress injury and provide rapid recovery of aerobic metabolism [24].

In France, Durandy et al. studied their results comparing intermittent warm blood cardioplegia (IWBC) and cold blood cardioplegia (CBC) in 1,400 patients with congenital heart disease. Their data indicate that IWBC is safe and effective compared to CBC and showed and that the use of IWBC resulted in a higher rate of resumption of normal sinus rhythm after crossclamp removal, shorter time to extubation and a decreased rise in Troponin I [25].

Allen et al. further conclude that in hypoxically stressed hearts that cold cardioplegia induction prevented further damage but did nothing to improve the deleterious effects of reoxygenation injury. However, several minutes of enhanced warm blood cardioplegia induction led to repair of the hypoxia/reoxygenation injury with preservation of myocardial function [12, 26].

Reperfusion

Ischemic injury during aortic crossclamp appears to be significantly exacerbated by reperfusion once the crossclamp is removed. Follette et al. studied the effects of ischemia and reperfusion on ischemic adult hearts and found that a brief period of warm blood cardioplegia prior to cross-clamp removal could ameliorate the reperfusion injury [27]. Kronon et al. showed that enriching terminal warm blood cardioplegia can facilitate a full myocardial recovery after a period of ischemia [26]. This is very significant since children are more prone to ischemia/reperfusion injury than adults [12, 13]. Toyoda et al. studied the cardioprotective effects of terminal warm blood cardioplegia and found that it resulted in an improvement in aerobic energy metabolism and a reduction in myocardial injury. They concluded that terminal warm blood cardioplegia should be used in all pediatric cardiac surgery [28].

Substrate and Electrolyte Enhancement

We know that the neonatal heart is very sensitive to extracellular calcium concentrations and that intracellular calcium accumulation during ischemia/reperfusion is injurious. Calcium mediated injury probably occurs as a result of increased ATP use, impaired ATP synthesis, activation of calcium-dependent degradative enzymes and calcium enhanced free radical-mediated injury. In a study of hypoxically stressed neonatal piglets, the addition of magnesium to normocalcemic blood cardioplegia was able to completely offset the deleterious effects of calcium mediated injury [29]. Interestingly, additional magnesium was found to have no cardioprotective effects when added to a hypocalcemic blood cardioplegia solution. Mechanistically, magnesium inhibits calcium entry across the cell membrane and displaces calcium from binding sites on the sarcoplasmic reticulum [12].

As mentioned earlier, the addition of the amino acids aspartate and glutamate are essential for the reparative ability of terminal warm blood cardioplegia [26]. Researchers continue to explore the optimal enhancing additives for cardioplegia solutions, ranging from nitric oxide and L-arginine supplements to an electrolyte composition that doesn't cause such a negative depolarizing effect on the myocardium [30, 31]. Much of this data remains to be studied and validated in clinical trials.

Infusion Methods

Most cardioplegia solutions are administered either antegrade through the aortic root or directly through handheld cannulas. There is a paucity of data regarding the use of retrograde cardioplegia in the pediatric population. Retrograde cardioplegia may be indicated in patients with severely depressed function or septal and ventricular hypertrophy, but there is no clear data to support its regular use in pediatric surgery.

The rate and pressure of delivery of antegrade cardioplegia is also seemingly important but rarely studied in pediatric cases. Most surgeons direct the rate of cardioplegia delivery by direct palpation of the aortic root or calculated pressures from perfusion. However, there is often a highly variable discrepancy between actual intravascular pressures and calculated pressures. Allen et al. studied the differential effects of using high pressure (80–100 mmHg) vs. low cardioplegia pressure (30–50 mmHg) in hypoxically stressed neonatal hearts. Their research showed that the low pressure delivery of cardioplegia was protective and resulted in complete preservation of myocardial and vascular endothelial function compared to the high pressure system which displayed increased levels of myocardial and endothelial dysfunction, increased myocardial edema and decreased ATP levels [12]. This method requires a transducible cardioplegia line or a direct intra-aortic pressure line to adequately assess cardioplegia infusion pressures.

Reoxygenation Injury

Chronically hypoxic neonatal hearts are very susceptible to oxygen-mediated injury when exposed to supranormal levels of oxygen [13]. Intuitively, the rapid reintroduction of high O_2 levels either via cardiopulmonary bypass or intubation and ventilation with 100 % FiO_2 would incite a deleterious "reoxygenation" effect. Allen et al. studied the effects of hypoxia followed by reoxygenation in hypoxic neonatal piglet hearts and concluded that abrupt reoxygenation caused an oxygen free-radical mediated injury with depressed myocardial function, increased pulmonary resistance and increased alveolar damage [13].

Because activated white blood cells are significantly involved in oxygen-mediated free radical injury after ischemia, Allen et al. found that the addition of a leukocyte-depleting filter in the bypass circuit eliminated the negative effects of abrupt reoxygenation injury. As a result, they strongly advocate a normoxic bypass strategy using a leukocyte-depleting filter in all patients with chronic hypoxia, myocardial hypertrophy or extremely high risk normoxic patients [13].

Conclusions

There has been an enormous amount of progress in the study of pediatric myocardial protection. This chapter attempts to highlight some of the advances regarding cardioplegia type and temperature and cardiopulmonary bypass strategy. Clearly, children are significantly different physiologically from adult cardiac patients. Myocardial protection strategies that we are accustomed to in the adult world are not easily translated to pediatrics. An understanding and willingness to embrace new techniques and strategies will be necessary to continue to advance the field of pediatric myocardial protection.

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Surgical Interventions for Congenital Heart Disease

23

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Abstract

Surgery for congenital heart disease encompasses a wide variety of procedures that are often performed in combination. Not all the operations are anatomic as some are physiologic to compensate for lesions in which an anatomic repair is not possible. Over the past decade, it has become apparent that the cumulative morbidity and mortality of palliative operations, followed by later repair, is greater than that of early reparative procedures. Primary reparative surgery in the neonate offers the opportunity to decrease the mortality and morbidity caused by the primary defect by preventing secondary damage to other organ systems. With further refinement of the timing and technique of cardiac surgery and postoperative care, there is likely to be future reduction in mortality rates for specific surgeries and secondary morbidity.

Keywords

Congenital heart disease • Cyanotic heart disease • Cardiopulmonary bypass

Introduction

Congenital heart disease (CHD) is the most common birth defect occurring in nearly 1 of 100 live births. The field of pediatric cardiac surgery has changed dramatically over the last several decades. Prior to the 1980s, children with CHD generally had either a surgical palliation or were "grown" over time prior to surgical repair. These practices were in part due to the lack of appropriately sized equipment for cardiopulmonary bypass and instruments to perform neonatal surgery. In addition, there was uncertainty over how neonates would fare undergoing open-heart repairs. Critical congenital heart defects that are uncorrected may cause progressive and irreversible secondary organ damage, principally to the heart, the lungs and the central venous system and may interfere with normal postnatal changes such as myocardial hyperplasia, coronary angiogenesis, and pulmonary vascular and alveolar development. As a result, many neonates with complex CHD did not survive to repair. In addition to the anatomic and functional sequelae noted, psychomotor and cognitive abnormalities are often present in the child with palliated or uncorrected critical CHD that may limit their ultimate development.

Surgery for CHD encompasses a wide variety of procedures that are often performed in combination. Not all the operations are anatomic as some are physiologic to compensate for lesions in which an anatomic repair is not possible. Over the past decade, it has become apparent that the cumulative morbidity and mortality of palliative operations, followed by later repair, is greater than that of early reparative procedures. Primary reparative surgery in the neonate offers the opportunity to

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decrease the mortality and morbidity caused by the primary defect by preventing secondary damage to other organ systems. With further refinement of the timing and technique of cardiac surgery and postoperative care, there is likely to be future reduction in mortality rates for specific surgeries and secondary morbidity.

Two Ventricle Repairs

Left-to-Right Shunt Lesions

Atrial Septal Defect

An atrial septal defect (ASD) is a communication between the left atrium and right atrium. Classification of ASDs depends upon their location in the septum. There are several anatomic types, including secundum, ostium primum, sinus venosus, and coronary sinus ASDs. Ostium secundum ASDs result from a defect in septum secundum. Ostium primum ASDs are a form of atrioventricular canal defect. The sinus venosus ASD is located either adjacent to the superior vena cava (SVC) or inferior vena cava (IVC) and is associated with partial anomalous pulmonary venous return of the right sided pulmonary veins. A coronary sinus ASD is the coronary sinus type that results from a lack of septation of the coronary sinus from the left atrium. It is often seen in conjunction with a left superior vena cava. Left-to-right shunting at the atrial level causes increases in right atrial and right ventricular volume and increased pulmonary blood flow. The degree of left-to-right shunting depends both on the size of the defect as well as on the relative compliance of the ventricles and degree of pulmonary hypertension.

Timing of Surgery

The majority of infants and children with ASDs are asymptomatic. Because congestive heart failure may occur in the second or third decade due to chronic right ventricular overload, closure is recommended during childhood. However, approximately 5 % of children may develop symptoms of congestive heart failure (CHF) prior to a year of age [1]. If patients exhibit early signs of CHF, the presence of mitral valve stenosis or left ventricular hypoplasia should be considered. Spontaneous closure of small secundum ASDs may happen during the first few years of life and therefore surgical closure is delayed until 3–5 years of age. When possible, children with secundum ASDs are considered for device closure by cardiac catheterization. However, ostium primum, sinus venosus, and coronary sinus ASDs require surgical closure and are not amenable to percutaneous intervention.

Method of Repair

Small secundum ASDs may be repaired directly with suture closure. Larger ASDs, primum ASDs and sinus venosus types require patch closure typically using native pericardium. Children with primum ASDs by definition have a common AV valve with a "cleft" in the left sided valve. Mitral valvuloplasty with closure of the cleft is recommended at the time of ASD closure to avoid progressive mitral regurgitation. Sinus venosus ASDs require atrial baffling of the right-sided anomalous pulmonary veins to the left atrium. Alternatively, a sinus venosus ASD may be repaired with a Warden procedure in which there is baffling of the anomalous right pulmonary veins to the left atrium and the superior vena cava is directly attached to the right atrial appendage.

Follow-up

Pericardial effusions are common after ASD repair, sometimes presenting weeks after surgery. Long-term complications are rare. Some children experience transient atrial arrhythmias or sinus node dysfunction postoperatively [2]. Postoperative evaluation should include ruling out superior vena cava or baffle obstruction or pulmonary vein stenosis in the case of sinus venosus ASD.

Ventricular Septal Defect

Ventricular septal defects (VSDs) are the most common form of CHD after bicuspid aortic valve and are categorized depending upon their location in the ventricular septum. Spontaneous closure rate depends upon the defect type. At The Children's Hospital of Philadelphia, the following classification system is used: muscular, conoventricular (perimembranous), inlet (AV canal), and conoseptal hypoplasia (supracristal, subpulmonary or outlet). Muscular and conoventricular defects are the most common types, accounting for approximately 80 % of all VSDs.

Timing of Surgery

Left-to-right shunting at the ventricular level results in left atrial and left ventricular volume overload and increased pulmonary blood flow. The degree of shunting depends on the size of the defect as well as the relative resistance between the pulmonary and systemic circulations. In the case of conoseptal and conoventricular VSDs, they may become restrictive as valve tissue, either aortic or tricuspid, partially obstructs the defect. Larger defects can become hemodynamically significant in the first 4–6 weeks of life. As the pulmonary vascular resistance falls in the first few weeks of life, left-to-right shunting increases and symptoms of CHF develop. Spontaneous closure can occur in the cases of muscular VSDs and less so with conoventricular VSDs [3]. Malalignment, inlet, and conoseptal hypoplasia VSDs rarely close spontaneously.

The symptomatic child with CHF and failure to thrive is repaired at presentation. Medical management includes diuretics and afterload reduction (typically with angiotensin-converting enzyme inhibitors). Malalignment and inlet VSDs

are typically closed during infancy and are found in conjunction with tetralogy of Fallot and common AV canal. Surgical closure is indicated if a patient develops aortic insufficiency due to prolapse of the aortic valve secondary to a Venturi or windsock effect of flow via the VSD, as closure of the VSD will minimize the progression of aortic insufficiency.

Method of Repair

Conoventricular, muscular and inlet VSDs are repaired via a right atriotomy whereas conoseptal hypoplasia is typically approached via the pulmonary artery. The tricuspid valve can be mobilized to facilitate exposure of the VSD [4]. If the VSD is a malalignment type, it is typically repaired via a right atriotomy, possibly in combination with a ventriculotomy when necessary to gain additional exposure. Small VSDs may be repaired by primary suture closure versus larger VSDs that typically require patch closure utilizing Dacron. In some patients with complex VSDs, repair may be delayed to allow growth and spontaneous closure. Pulmonary artery banding is rarely indicated but used to control pulmonary blood flow in those infants with multiple or "swiss-cheese" defects.

Follow-up

Surgical mortality for VSD closure is less than 1 %. Up to 5 % of patients undergoing VSD closure may suffer from injury to the conduction system. Complete heart block is a rare complication. Temporary pacing is used to treat conduction disorders postoperatively for up to 7 days prior to implantation of a permanent pacing system in case of delayed return to spontaneous sinus rhythm. Residual VSDs are located on intraoperative transesophageal echocardiogram and usually tolerated if less than 3 mm in size [5]. Cardiac catheterization can be used to accurately determine the relative left to right shunt from a residual defect.

Patent Ductus Arteriosus

A patent ductus arteriosus (PDA) is a vascular communication between the aorta just distal to the left subclavian artery and the pulmonary artery. Left-to-right shunting at the ductus results in increased pulmonary blood flow with left atrial and ventricular enlargement due to volume overload. Again, the degree of shunting is relative to the size of the communication and the relative difference between pulmonic and systemic circulations.

Timing of Surgery

Medical management includes diuretic administration for the treatment of a hemodynamically significant left to right shunt and indomethacin or ibuprofen therapy to induce ductal closure [6]. Indomethacin is a cyclooxygenase-1 (COX-1) receptor inhibitor and causes vasoconstriction of the ductus typically administered in three doses within 24 h. If indomethacin or ibuprofen are contraindicated or fail to close the ductus, percutaneous or surgical ligation is indicated and can be performed with minimal morbidity and mortality [7]. There is abundant controversy surrounding timing of closure in neonates [8]. In symptomatic term infants, closure is indicated when either CHF or failure to thrive is present. In patients who are asymptomatic, surgical closure is performed to avoid the development of endocarditis or late pulmonary vascular disease.

Method of Repair

Options for ductal closure include transcatheter device occlusion, surgical ligation via thoracotomy with either extra-or intra-pleural dissection, or video-assisted thoracoscopic surgery [9]. Transcatheter closure is appropriate for older infants, children and adults. In preterm infants, ligation without division is recommended due to the relative fragility of the tissue.

Follow-up

In isolated PDAs in which complete closure has been documented, no follow-up is needed unless recanalization is suspected. Mediastinal complications include phrenic or recurrent laryngeal nerve paralysis manifested as difficulty swallowing and a hoarse voice, hemothorax, pneumothorax, chylothorax and significant bleeding [10].

Common Atrioventricular Canals

The endocardial cushions form the atrioventricular (AV) valves and septum. The normal AV canal septum fuses with the lower portion of the atrial septum and the upper portion of the ventricular septum, thereby dividing the canal into two atria and two ventricles. As a result of failure of the endocardial cushions to join, a common atrioventricular canal (CAVC) forms. Lesions associated with AVC defects include patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, heterotaxy syndrome, a left superior vena cava and, less commonly, a propensity towards late development of subaortic stenosis. It is commonly associated with trisomy 21. Canals are characterized via Rastelli classification based upon their chordal attachments to the ventricular septum. Incomplete AVC have no VSD component. Transitional AVC have a small VSD component. Surgical repair is based upon closure of the defects with AV valve reconstruction and suspension on the VSD portion of the patch.

Timing of Surgery

Symptomatic patients are typically repaired at the age of presentation. Asymptomatic children may undergo elective repair between 6 months and 1 year of age prior to the development of significant pulmonary vascular disease and

pulmonary hypertension. Patients with transitional canal are typically asymptomatic and may be repaired at a later age. Pulmonary vascular disease is common, particularly in those patients with trisomy 21.

Method of Repair

Medical management of heart failure in the first few months of life is targeted towards optimizing weight gain. Repair of the CAVC involves closure of the VSD, the primum ASD and the cleft in the left AV valve. The septal defects are closed by either a one or 2-patch technique to divide the common canal into appropriate left and right sides. Typically the VSD is closed with Dacron and the ASD closed with a pericardial patch if the 2-patch technique is utilized. Suture closure of the cleft is performed with great care not to narrow the inflow to the left ventricle. It is preferable to leave left AV valve regurgitation opposed to stenosis, thus partial closure of the cleft is performed when complete closure is not possible.

Follow-up

While surgical mortality is low, patients with CAVC are subject to all the complications related to both ASD and VSD closure. Arrhythmias in the perioperative period are common, including sinus node dysfunction. Pulmonary hypertension postoperatively is common in both trisomy 21 and older patients [11, 12]. A minority of patients will require re-intervention upon the left AV valve for significant AV valve regurgitation [13, 14].

Aorticopulmonary Window

An aorticopulmonary (AP) window is a conotruncal defect between the aorta and the pulmonary artery. The defect may be either proximal or distal to the pulmonary bifurcation. It is distinct from truncus arteriosus in that two separate semilunar valves are present. An AP window may be associated with ventricular septal defects, coarctation of the aorta or interrupted aortic arch.

Timing of Surgery

Left-to-right shunting leads to increased pulmonary vascular blood flow and left sided volume overload. Neonates usually present in the first month of life after the pulmonary vascular resistance falls and the pulmonary blood flow increases, resulting in CHF. These lesions are repaired at the time of diagnosis.

Method of Repair

Surgical closure of an AP window is approached through a midline sternotomy. The repair requires incision in the aorta, in the pulmonary artery or directly into the window. A patch is used to close the defect and typically the incision is closed to incorporate the patch [15].

Follow-up

The prognosis is excellent if surgical correction is performed early in life. Residual deficits are rare and pulmonary vascular changes are rare unless the patient had long-standing left-right shunting and pulmonary hypertension.

Mixing Lesions

Truncus Arteriosus

Truncus arteriosus is a relatively rare conotruncal defect defined as a single arterial vessel that originates from the heart and gives rise to the coronary arteries, pulmonary arteries, and aortic arch vessels. There is typically a malalignment VSD present. There are four major types, classified by Collett and Edwards and modified by Van Praagh, distinguished by the origin of the pulmonary arteries and the distal arch anatomy. Most commonly, the pulmonary arteries both arise from the common arterial trunk. Type IV includes interrupted aortic arch and is found in approximately 20 % of patients with truncus arteriosus [16]. The truncal valve usually has three leaflets but may include as many as six. The valve is often dysmorphic and there may be truncal stenosis or regurgitation. Truncus arteriosus is often associated with a right sided aortic arch. Extracardiac and genetic anomalies are often seen such as 22q11 deletion that occurs in up to 40 % of these patients.

Timing of Surgery

Once patients experience a fall in pulmonary vascular resistance they develop significant left to right shunting and become symptomatic; presenting in the first few weeks of life with CHF and failure to thrive. If left untreated, the lesion carries a significant mortality of 90 % by 1 year of age. This is attributable to pulmonary over-circulation and the development of pulmonary hypertension. Most children are repaired upon presentation in the neonatal period [17].

Method of Repair

Surgical repair includes patch closure of the VSD, removal of the pulmonary arteries from the common trunk, followed by closure of the aortic defect and insertion of a conduit from the right ventricle to the pulmonary arteries. The defect in the aorta may be repaired either primarily or with a patch. A ventriculotomy is used to expose the VSD for closure and provide a location for placement of the proximal conduit. If significantly regurgitant, repair of the truncal valve is performed at this time.

Follow-up

Surgical mortality may approach 10 % with increased risk in older patients or those with severely dysplastic truncal valves

with hemodynamically significant regurgitation, genetic syndromes or aortic arch obstruction [18, 19]. Postoperative care is determined by the degree of truncal valve disease, the presence of a residual ventricular septal defect, and the need for conduit replacement [20]. Pulmonary hypertensive crises may occur as well as arrhythmias. Late reoperations are necessary for conduit revisions at a minimum.

Total and Partial Total Anomalous Pulmonary Venous Connection

Total anomalous pulmonary venous connection (TAPVC) and partial anomalous pulmonary venous connection (PAPVC) involve aberrant drainage of one or all pulmonary veins into a systemic venous structure rather than into the left atrium. TAPVC is characterized by the location of drainage of the veins as either supracardiac, infracardiac, cardiac, or mixed. In both the supra-and infracardiac types, the pulmonary veins drain to a confluence behind the heart and then drain via an anomalous vein into the systemic circulation, typically into the innominate vein or SVC or into the IVC, respectively [21]. When obstructed, pulmonary venous hypertension develops, resulting in hypoxemia, pulmonary edema, and pulmonary hypertension. If unobstructed, the lesion is similar physiologically to an ASD. PAPVC varies in presentation and is often associated with a sinus venosus ASD. Scimitar is a unique form of PAPVC in which the right pulmonary vein drains into the right-sided inferior vena cava and is associated with pulmonary sequestration and hypoplasia and aortopulmonary collaterals.

Timing of Surgery

In patients with obstructed TAPVC, repair is performed at the time of presentation. Infants with TAPVC may present acutely and with severe decompensation. For those infants with unobstructed TAPVC, typically cardiac, repair is performed when the symptoms of CHF appear. For patients with PAPVC, repair most often occurs when the typical ASD is repaired electively.

Method of Repair

In both the supra- and infracardiac types of TAPVC, the confluence posterior to the heart is opened widely and anastomosed in a sutureless fashion to the back of the left atrium. In this technique the pulmonary veins proper are not sutured but, instead the pericardium covering the confluence is sutured. There is no consensus on whether the vein that drains the confluence to the systemic vein should be ligated. For cardiac TAPVC, the coronary sinus is widely opened and the veins baffled to the left atrium with closure of the ASD. Mixed TAPVC is closed with a variety of techniques depending upon the lesion. PAPVC is repaired in conjunction with a sinus venosus ASD or by separate inclusion techniques into the left atrium depending upon the affected vein or veins.

Follow-up

Postoperative care is challenging mainly due to the presence of pulmonary hypertension, which is a significant risk factor for death [22]. Paroxysmal severe pulmonary hypertension crises are managed by the use of neuromuscular blockade and inhaled nitric oxide in the perioperative period. Residual venous obstruction is possible and must be assessed by echocardiogram. If necessary, cardiac catheterization with balloon dilation of the affected vessels is performed. Patients remain at risk for long-term pulmonary venous obstruction as well.

D-Transposition of the Great Arteries

Transposition of the great arteries (TGA) is defined as the rightward and anterior aorta arising from the anatomic right ventricle and the pulmonary artery from the anatomic left ventricle, also known as ventricular-arterial discordance. D-transposition of the great arteries (D-TGA) is the most common form. In this case, deoxygenated blood is ejected from the right ventricle to the aorta and oxygenated blood from the lungs is circulated via the left ventricle to the pulmonary circulation. Mixing of the blood must occur at a minimum via one of three levels: the PFO (ASD), VSD, or PDA. Anomalies associated with D-TGA include VSD, coronary artery anomalies, aortic arch obstruction, or left ventricular outflow tract obstruction [23]. Only 10 % of patients have a coexisting extracardiac anomaly. Untreated, 90 % of infants will die within the first year of life.

Timing of Surgery

Corrective surgery is performed within the first week of presentation during the neonatal period. In D-TGA with intact ventricular septum, despite the use of prostaglandin therapy, there is typically inadequate mixing at the atrial level and patients present cyanotic. In cases with severe cyanosis with an open ductus arteriosus, a balloon atrial septostomy is performed to increase left to right shunting at the atrial level to improve systemic saturations. Surgical repair is undertaken once the patient is stabilized.

Method of Repair

In the 1960s, the atrial switch became the first successful procedure for D-TGA associated with long-term survival. Although the arterial switch was attempted in the same era, mortality for this procedure was initially extremely high. The trend towards the arterial switch began in the 1980s once surgeons improved the coronary artery transfer technique.

Atrial inversion procedures such as the Mustard and Senning operations involve baffling the pulmonary venous flow to the tricuspid valve (systemic circulation) and the systemic venous flow from the SVC and IVC to the mitral valve (pulmonary circulation), leaving the right ventricle as the systemic pumping chamber. Although previously the principal surgical procedure for D-TGA, atrial switch is now reserved for those high-risk patients with significantly abnormal pulmonary valves (i.e. the neo-aortic valve after the arterial switch), challenging coronary artery anatomy, or late diagnosis (greater than a few months of age).

In the present era, children with D-TGA without significant right ventricular outflow tract obstruction or left ventricular outflow tract obstruction and suitable coronary artery anatomy undergo an arterial switch operation (ASO). In the ASO, the aorta and the pulmonary artery are transected above their respective semilunar valves and switched with reimplantation of the coronary arteries into the aorta. The distal main pulmonary artery is passed over anterior to the aorta in the leCompte maneuver and connected to the proximal native aortic root, which becomes the neo-pulmonary root. The ASO is usually performed in the first few weeks of life. If performed after the pulmonary vascular resistance falls, the left ventricle must be prepared to take on the systemic pressure by banding the pulmonary artery for several weeks.

More complex surgical intervention is required for D-TGA with malalignment VSD with right or left ventricular outflow tract obstruction. In those with left ventricular outflow tract obstruction and pulmonic stenosis, the Rastelli operation is a surgical option. In this case, the proximal main pulmonary artery is divided and oversewn, the left ventricular output is baffled to the aorta by placement of a patch from the left ventricle to the aorta, and the right ventricle is connected to the main pulmonary artery by a homograft conduit. The VSD must be adequate in size to permit unobstructed blood flow from the left ventricle to the aorta and this often necessitates enlargement of the VSD in some cases by anterior excision of septal muscle. If right ventricular outflow tract obstruction occurs in association with TGA/VSD, the VSD is closed with a patch, the right ventricular outflow tract is enlarged by a transannular patch and the distal arch is repaired if necessary.

Follow-up

Perioperative and long-term follow-up are variable, depending upon the preoperative anatomy and the surgery performed. The long-term consequences of the atrial switch operation have become evident with time. The extensive atrial surgery required for this procedure often results in significant scar tissue and subsequent arrhythmias including sick sinus syndrome, atrial flutter, and atrial fibrillation. Frequently, a pacemaker is required for sinus node dysfunction and bradyarrhythmias. In addition, because the right ventricle performs as the systemic pumping chamber, right ventricular failure and tricupsid regurgitation are common.

The ASO is generally associated with excellent outcomes in most surgical centers, and the repair is physiologic in that the left ventricle pumps to the aorta [24, 25]. In rare cases, myocardial ischemia may occur in the postoperative period, particularly when the coronary arteries come from one orifice (single coronary) or course through part of the aortic wall (intramural course). Long-term issues include coronary insufficiency (stenosis after reimplantation), neo-aortic valve regurgitation (native pulmonary valve), neo-aortic root dilation, and supravalvar pulmonary stenosis at the site of the pulmonary artery anastamosis. The supravalvar PS results from compression of the pulmonary arteries by the posterior aorta, circumferential narrowing at the suture line, or branch pulmonary artery stenosis. There is a small but real risk of sudden death from coronary ischemia. After Rastelli repair, right ventricle to pulmonary artery conduit replacement is often required as the patient grows. In some cases, the VSD (pathway from the left ventricle to the aorta) becomes restrictive, resulting in sub-aortic stenosis that may require revision. Complete heart block may occur in rare cases secondary to enlargement of the VSD to create an effective LV to aortic baffle.

Congenitally Corrected Transposition of the Great Arteries

In congenitally corrected transposition of the great arteries (L-TGA), the pulmonary artery is connected to the left ventricle and the aorta is connected to the right ventricle. The ventricles are L-looped (i.e. reversed in position). As a result, desaturated blood returns to the right atrium, enters the left ventricle, and is ejected into the pulmonary arteries. Oxygenated blood returns to the left atrium, enters the right ventricle and then is ejected to the body through the aorta. Thus, the circulation remains in series, but the anatomic right ventricle acts as the systemic pumping chamber. Patients with L-TGA may also have ventricular septal defect, Ebstein's anomaly of the left-sided AV valve, pulmonary stenosis, complete heart block, or a combination thereof.

Timing of Surgery

Historically, patients with L-TGA did not have surgery performed unless the pulmonary stenosis or Ebstein's valve needed to be addressed. Young patients are candidates for the double switch operation consisting of both an atrial and arterial switch to decrease the risk of right ventricular failure in the long term. The timing of this complex surgical procedure is usually quite variable.

Method of Repair

Many patients will undergo an anatomic repair in which the right ventricle will remain the systemic ventricle. For these patients surgical intervention is focused on VSD closure or tricuspid valve repair or replacement. The double switch operation is a combination of the atrial level and arterial level switch operations. The goal of the double switch operation is to restore the left ventricle as the systemic pumping chamber (physiologic repair). If one of the chambers is hypoplastic, the alternative is to perform a Fontan palliation.

Follow-up

As L-TGA is a rare form of CHD with a variety of clinical manifestations that are not always surgically treated, optimal surgical management remains controversial. Eventually, it is believed that the systemic right ventricle will manifest failure with significant tricuspid regurgitation, especially if the left-sided tricuspid valve is Ebsteinoid. It remains unclear whether the double switch operation will afford less long-term morbidity. Similar issues arise as discussed after the atrial and arterial switch operations.

Left-Sided Obstructive Lesions

Left-sided obstructive lesions present as a spectrum of diseases involving hypoplasia of left-sided structures. Frequently, multiple levels of obstruction are seen in association with one another, such as aortic stenosis and coarctation of the aorta. Shone's complex is a combination of defects including supravalvar mitral ring (which may cause mitral stenosis), subaortic stenosis, and coarctation of the aorta. Each lesion will be discussed individually; hypoplastic left heart syndrome will be discussed under the section titled: "Single Ventricle Repairs". These lesions may be ductal dependent, and upon closure of the ductus arteriosus affected neonates may present with shock or circulatory collapse.

Aortic Stenosis

Morphologic abnormalities of the aortic valve may range from a bicuspid aortic valve with little stenosis or regurgitation to a unicommissural, myxomatous severely obstructive valve with severe left ventricular outflow tract obstruction. Aortic stenosis may occur at the level of the annulus, the supravalvar level (in Williams syndrome), or the subvalvar level. In the most severe cases of aortic stenosis, there is severe dysfunction of the left ventricle, endocardial fibroelastosis (i.e. ischemia of the endocardium), and mitral of left ventricular hypoplasia (or both) [26]. Critical aortic stenosis is defined as severe valvular aortic stenosis with ductal dependent systemic blood flow.

Timing of Surgery

Critical aortic stenosis requires treatment at the time of presentation. Initial management includes treatment of shock, airway management, inotropic support and, most importantly, initiation of prostaglandin therapy. Depending on the constellation of associated anomalies and the severity of left ventricular dysfunction, treatment for severe aortic stenosis may include balloon dilation valvuloplasty or surgical valvotomy, Stage I Norwood palliation, a neonatal Ross or Ross-Konno procedure, or cardiac transplantation [27, 28]. Non-critical aortic valve stenosis is usually addressed by balloon dilation valvulopasty, when the mean gradient across the aortic valve by echo or the peak-to-peak gradient by cardiac catheterization reaches 50 mmHg, or when there is evidence of left ventricle dysfunction or other symptomatology such as decreasing exercise tolerance. In addition, aortic valve stenosis may be addressed at any time during childhood or adolescence by surgical valvotomy or valvuloplasty, or valve replacement.

Method of Repair

For isolated aortic stenosis, in which balloon dilation valvuloplasty has not adequately relieved the stenosis or resulted in moderate or greater aortic insufficiency, various surgical approaches may be utilized including surgical valvotomy or valvuloplasty; or valve replacement with autograft (i.e. Ross or Ross Konno procedures), mechanical, homograft, or xenograft valves.

In cases in which there is severe aortic stenosis or regurgitation, a Ross or Ross-Konno procedure may be performed. In the Ross procedure, the pulmonic valve is excised and replaced with an RV-PA conduit. The aortic valve is excised and the native pulmonic valve is then implanted as an autograft into the aortic position. The coronary arteries are excised from the native aorta and reimplanted into the pulmonary autograft. In cases in which there is both aortic valve and subaortic stenosis, the Konno modification is added to relieve the subaortic stenosis. The Konno consists of dividing the interventricular septum to place a patch to enlarge the left ventricle outflow tract. The Ross operation is an alternative to prosthetic aortic valve replacement and has the advantages of potential growth of the subaortic area as the patient grows [28]. Additionally, it does not require anticoagulation.

Follow-up

Children with aortic stenosis require close follow-up for evidence of increasing left-sided obstruction, aortic insufficiency, or both. Repeat procedures during the first year of life are required if significant obstruction recurs. Children who have had a Ross or a Ross-Konno procedure must also be followed for evidence of conduit obstruction, coronary artery insufficiency, neo-aortic root dilation and regurgitation. Prosthetic valve replacement is required if the Ross fails or if

the native pulmonary valve is abnormal. Non-Ross aortic valve replacement requires anticoagulation. Anticoagulation levels need to be followed on a regular basis to minimize the risk of thromboembolic complications.

Coarctation of the Aorta

Coarctation of the aorta is defined as a discrete narrowing of the thoracic aorta. Coarctation of the aorta typically results in a narrowing of the upper thoracic aorta, caused by posterior infolding or indentation opposite the ductus arteriorus insertion site. In neonates, coarctation of the aorta is commonly associated with hypoplasia of the transverse aortic arch and/or ventricular septal defect [29]. Critical coarctation of the aorta (i.e. ductal dependent systemic blood flow) presents similarly to other critical left-sided obstructive lesions, with cardiovascular collapse and shock after closure of the ductus arteriosus. The clinical presentation of coarctation of the aorta in the neonatal period varies from profound shock, metabolic acidosis and end-organ ischemia to slow progressive CHF. Older children often present with systemic hypertension and a blood pressure gradient from the upper to the lower extremities.

Timing of Surgery

Repair of symptomatic patients is done at the time of presentation. In general, neonates who present with cardiovascular collapse are repaired after stabilization with prostaglandin E_1 and recovery of end-organ function. Ideally, in the asymptomatic patient, repair should be undertaken before 1 year of age. Persistent systemic hypertension is less likely to occur in children repaired before 1 year of age. The asymptomatic neonate with coarctation is usually repaired after the first month of life to minimize the risk of recoarctation [30]. Older children and young adults are usually repaired at the time of diagnosis.

Method of Repair

Treatment options include percutaneous balloon angioplasty with or without stent placement and surgical repair. During balloon dilation, there is a physical disruption of the intimal and medial layers of the aorta. Due to the nontrivial incidence of aortic aneurysm formation and recoarctation with primary balloon angioplasty, most large centers generally manage native coarctation of the aorta with surgery [31, 32]. Surgical options include resection and end-to-end anastomosis, end-to-side anastomosis, subclavian flap angioplasty, and patch aortoplasty [33, 34]. Repair of coarctation of the aorta is accomplished through a posterolateral thoracotomy incision. In the technique of resection with extended end-to-end anastomosis, the aorta is mobilized from pleural and fascial attachments to enable clamps to be placed proximal to the origin of the left common carotid artery and postductally on the descending aorta. The incision is extended to the inferior wall or lesser curvature of the aortic arch and the posterior wall or greater curvature of the descending aorta to create an extended anastomosis. Cardiopulmonary bypass is not necessary in the vast majority of cases. However, in the cases of severe transverse arch hypoplasia, the repair is performed using deep hypothermic circulatory arrest via a sternotomy incision.

Follow-up

The immediate postoperative evaluation should include assessment for residual obstruction, low cardiac output, spinal cord ischemia, and injury to structures adjacent to the aortic arch. Phrenic nerve palsy or paresis can lead to hemi-diaphragmatic paralysis and recurrent laryngeal nerve damage can cause stridor, hoarseness and aphonia [35]. Disruption of the thoracic duct may results in chylothorax. Hypertension may persist after repair due to arterial compliance, vascular reactivity and baroreceptor function.

Residual or recurrent obstruction is sometimes observed, particularly in neonates and infants. If residual coarctation occurs with no clinical symptoms, balloon dilation 2 months after repair is recommended. The procedure is delayed to allow proper wound healing of the suture line. Spinal cord ischemia is a catastrophic complication that occurs rarely, particularly in neonates and infants. This complication may be a result of inadequate collateral circulation to the anterior spinal artery [36]. Typically, stent placement is reserved for adolescents and adults. In rare cases in adults, recoarctation is treated with a surgical extraanatomic bypass or interposition graft.

Interrupted Aortic Arch

Interrupted aortic arch (IAA) results from a disconnection between the ascending and descending aorta and may be divided into several types depending upon where the interruption occurs. Perfusion to the lower extremities is provided by the ductus arteriosus. IAA may be associated with truncus arteriosus, aorticopulmonary window, double-outlet right ventricle and single ventricle complexes. In IAA Type A, aortic interruption occurs just distal to the left subclavian artery and is associated with transposition of the great arteries. In IAA Type B, aortic interruption occurs between the left carotid and subclavian arteries and is associated with posterior malalignment VSD and subaortic stenosis. Many of these patients have 22q11 deletion, particularly if the arch is right sided. In IAA type C, aortic interruption occurs proximal to the left carotid is extremely rare.

Timing of Surgery

The clinical presentation and preoperative management of IAA is similar to critical coarctation of the aorta. Prostaglandin E_1 (PGE_1) is used to maintain ductal patency until surgical repair is performed. Systemic blood flow to the lower body is maintained via the ductus arteriosus.

Method of Repair

In most cases, arch reconstruction can be accomplished by end-to-end anastomosis as in repair of coarctation of the aorta [37]. In some cases, patch augmentation or a conduit may be required to connect the ascending and descending aorta. If present, a VSD is generally closed with a patch during the same operation. If the left ventricular outflow tract is too small to support he systemic circulation then a Ross-Konno is indicated. If transposition of the great arteries is also present a concurrent arterial switch operation is performed.

Follow-up

The long-term issues associated with the care of patients with interrupted aortic arch are similar to those of coarctation of the aorta. In addition, if the subaortic region is small, subaortic stenosis may develop over time and require another operation to repair [38].

Mitral Stenosis and Cor Triatriatum

Congenital mitral stenosis in isolation is rare. It is generally seen in association with other left-sided lesions. It may occur due to congenital abnormalities of the annulus, the leaflets, chordae, and/or papillary muscles. There are two main subtypes: parachute mitral valve, in which the chordae tendinae insert into only one papillary muscle, and mitral valve arcade in which the mitral valve leaflets insert directly into the papillary muscles with no chordae creating limited leaflet excursion. Often, mitral valve hypoplasia is seen in combination with these anomalies. The main physiologic consequences are pulmonary edema and pulmonary arterial hypertension, potentially resulting in right ventricular failure. Cor triatriatum is defined as a membranous diaphragm in the left atrium that separates the pulmonary venous return from the mitral valve orifice. For both mitral stenosis and cor triatriatum, pulmonary venous obstruction can cause pulmonary hypertension.

Timing of Surgery

As surgical options for mitral stenosis are limited, repair is reserved for the symptomatic patient or the patient who manifests pulmonary arterial hypertension. Delaying repair is ideal, particularly if mitral valve replacement is likely. Cor triatriatum should be addressed surgically in the symptomatic patient.

Method of Repair

Mitral stenosis is difficult to treat because valvuloplasty often results in either residual mitral obstruction or the development of significant mitral regurgitation. Correction of associated lesions that may increase flow across the mitral valve (i.e. VSD or PDA) may lessen the severity of the mitral stenosis, delaying the need for intervention on the valve. If intervention is warranted but the mitral valve is not deemed repairable, mitral valve replacement is an alternative option. Ideally, mitral valve replacement should be delayed until a child is large enough for the valve to be placed in the annulus. However, if an infant is critically ill, placement of a prosthetic mitral valve in the supra-annular position (within the left atrium) is a viable option. Cor triatriatum is surgically repaired by resection of the membrane from the left atrium. This procedure is generally associated with an excellent result.

Follow-up

Patients who undergo mitral valvuloplasty require close follow-up to assess the mitral valve for restenosis or the development of mitral regurgitation. Mitral valve replacement is generally performed using a prosthetic valve. Lifelong anticoagulation is required to prevent thrombosis. Follow-up echocardiograms are helpful to assess the valve for perivalvar leak and stenosis. Indeed, as the child grows, re-replacement of the mitral valve may be required.

Right-Sided Obstructive Lesions

Right-sided obstructive lesions vary in severity from mild pulmonic stenosis to tetralogy of Fallot with pulmonary atresia with aortopulmonary collaterals providing pulmonary blood flow. Pulmonary outflow obstruction can be seen in patients with other conotruncal anomalies such as double-outlet right ventricle, or single-ventricle lesions.

Pulmonic Stenosis

Pulmonic valve stenosis is characterized by thickened, doming pulmonary valve leaflets with a hypertrophied right ventricle and a normal tricuspid valve annulus. Critical pulmonary stenosis is defined as severe valvular pulmonic stenosis with duct-dependent pulmonary blood flow.

Timing of Surgery

Critical and symptomatic pulmonic stenosis is addressed at presentation. In asymptomatic older patients, intervention is generally recommended when the right ventricular pressure exceeds 50 mmHg or three-quarters systemic pressure [39]. It is also frequently addressed if the patient is cyanotic or if another lesion, such as a VSD requires intervention.

Method of Repair

Balloon valvuloplasty in the cardiac catheterization laboratory remains the initial procedure of choice for valvar pulmonic stenosis. In some patients with a dysplastic pulmonary valve (i.e. Noonan's syndrome), surgical valvotomy may be necessary. After either procedure, a small right-to-left shunt may persist at the atrial level until right ventricular hypertrophy regresses and compliance improves.

Follow-up

Patients must be followed closely for recurrent stenosis of the valve, and they occasionally require reintervention. Pulmonic regurgitation following valvotomy or valvuloplasty is generally well tolerated in the absence of significant tricuspid insufficiency. Patients with severe regurgitation must be assessed frequently for progressive right ventricular dilation or dysfunction.

Tetralogy of Fallot (TOF)

Although characterized as having four components (i.e. malalignment VSD, pulmonic stenosis, right ventricular outflow hypertrophy, and overriding aorta), TOF is primarily a single conotruncal defect, namely anterior malalignment of the infundibular septum. This results in an unrestrictive malalignment VSD and a narrowing of the pulmonary outflow tract, a combination that leads to right ventricular hypertrophy. Furthermore, due to the malalignment VSD, the aorta, although actually in the normal position, appears to be overriding the ventricular septum. TOF is associated with several genetic syndromes including Trisomy 21 and 22q11 microdeletion. Up to 25 % of patients with TOF may have 22q11 microdeletion. The anatomy and physiology of TOF is extremely variable including TOF with pulmonary atresia, TOF with CAVC, and TOF with absent pulmonary valve leaflets.

Typical TOF

Timing of Surgery

Controversy still exists regarding the surgical management of patients with TOF. In asymptomatic children, elective repair is recommended at 3–6 months of age or prior to evidence of "hypercyanotic spells". A "hypercyanotic spell" is an indication for non-elective repair. For symptomatic neonates with significant obstruction to pulmonary blood flow (i.e. critical pulmonary valve stenosis), palliation with prostaglandins is recommended to provide adequate pulmonary blood flow. Some centers have pursued a staged repair consisting of a Blalock Taussig shunt during the neonatal period or infancy followed by complete repair later. However, in the current era, neonatal complete repair for symptomatic neonates is commonly performed.

Method of Repair

If there is significant pulmonary valve hypoplasia, TOF repair involves a transannular patch. This enlarges the outflow tract to extend both below and above the annulus of the pulmonary valve. The transannular patch disrupts the native valve thus resulting in pulmonary regurgitation, which is generally well tolerated in children. Occasionally, if the right ventricular outflow tract is well developed, a transannular patch is not necessary and every effort is made to preserve pulmonary valve competency. The malalignment VSD is closed with a Dacron patch.

Follow-up

For elective TOF repair, surgical mortality is low. In the immediate perioperative period, right-heart diastolic dysfunction can be seen because the right ventricular hypertrophy takes time to regress. In some cases, both systolic and diastolic dysfunction can be severe and the patient develops symptoms of low cardiac output. Over the long term, patients with TOF must be followed closely for right ventricular dilation secondary to pulmonary regurgitation, branch pulmonary artery stenosis, or both. TOF patients have an increased risk for sudden death from ventricular arrhythmias later in life, which may be related to RV volume overload, residual RV outflow tract obstruction, ventricular scarring, or a combination thereof.

TOF with Pulmonary Atresia

TOF with pulmonary atresia (TOF/PA) has also been referred to as PA with ventricular septal defect (PA/VSD). TOF/PA is an extremely heterogenous defect because of the variability of the pulmonary architecture. Usually severe infundibular hypoplasia and valve atresia exists. When evaluating the pulmonary arteries, three subgroups of TOF/PA emerge.

1. Confluent "true" pulmonary arteries, close to normal in caliber perfused by the patent ductus arteriosus.
2. Small "true" pulmonary arteries and multiple aortopulmonary collateral arteries (MAPCAs) with multiple segments of lung receiving dual supply.
3. Absent or extremely diminutive "true" pulmonary arteries, less than 2 mm, with MAPCAs.

Timing of Surgery

Initial management depends upon the source of pulmonary blood flow as well as the size and branching pattern of the distal pulmonary arteries. In neonates with confluent "true" pulmonary arteries, prostaglandin E_1 will ensure pulmonary

blood flow until either a palliative aortopulmonary shunt or a complete repair can be performed.

Method of Repair

For patients with confluent "true" pulmonary arteries, a complete repair consists of VSD closure and establishment of unobstructed flow from the right ventricle to the pulmonary arteries, either with a conduit or with a patch. Complete repair is dependent upon the size of the pulmonary arteries and the infundibulum. In some cases, a transannular patch is possible versus use of a right-ventricular to pulmonary artery conduit. The therapeutic approach to the other two subgroups, in which MAPCAs are present, involves establishing forward flow into the "true" pulmonary arteries, followed by angiography to determine the segments of the lungs that are supplied by the "true" pulmonary arteries, the MAPCAs alone, or both. Surgical options to establish flow into the "true" pulmonary arteries include an aortopulmonary shunt, a direct connection of the back of the aorta to the diminutive central pulmonary arteries, or a right ventricle to pulmonary artery conduit. Segments supplied by the MAPCAs may need to be connected or "unifocalized" to the "true" pulmonary arteries [40]. In theory, this forward flow allows the pulmonary arterial supply to grow as the child grows. Often the VSD is left open until branch pulmonary arteries are of adequate size. Once the cross-sectional area of the pulmonary vascular bed is sufficient to allow a normal cardiac output through the "true" pulmonary arteries without significantly elevated right ventricular pressure, closure of the ventricular septal defect is performed.

Follow-up

In those patients with TOF and good-sized branch pulmonary arteries, outcome is similar to those with the typical form of TOF. In those with diminutive pulmonary arteries, the unifocalized arteries often become stenotic over time. These patients frequently require serial cardiac catheterizations with balloon angioplasty of the affected segments. In general, outcome for the group of TOF patients with MAPCAs is poor over the long term, and there is controversy over whether aggressive intervention is warranted. Right ventricular hypertension with an inadequate pulmonary vascular bed is common.

TOF with Absent Pulmonary Valve Syndrome

TOF with absent pulmonary valve (TOF/APV) is a variant of TOF marked by dysgenesis of the pulmonary valve, which is severely malformed and incompetent, annular stenosis, and severe pulmonary regurgitation. All cases are associated with a large VSD. Massive enlargement of the branch pulmonary arteries is common due to in-utero pulmonary regurgitation. Tracheobronchomalacia is typically present and thought to be due to compression from the massive branch pulmonary arteries.

Timing of Surgery

Neonates with TOF/APV typically present soon after birth with severe respiratory distress, cyanosis and hyperinflation caused by tracheobronchial compression. Repair is usually undertaken in the first few days to weeks of life.

Method of Repair

Repair of this defect includes VSD closure, placement of a monocusp or a valved homograft in the right ventricular outflow tract to minimize pulmonary regurgitation and plication of the pulmonary arteries [41, 42].

Follow-up

Despite adequate repair, symptomatic neonates often continue to have airway problems. The clinical spectrum varies from mild bronchospastic disease to ventilator dependence that requires tracheostomy and chronic mechanical ventilation.

Double Outlet Right Ventricle

This conotruncal lesion is not discussed in detail in this chapter. There is a tremendous amount of variability in double outlet right ventricle (DORV). Both great vessels arise from the right ventricle and the only outflow from the left ventricle is through the VSD. DORV can mimic the physiologies of various other anatomies including VSD, TOF, or TGA/VSD. The VSD in DORV can be subaortic like a VSD or subaortic with pulmonary stenosis similar to TOF, subpulmonic similar to the Taussig Bing variety of TGA/VSD, under both great vessels ("doubly committed"), or not committed to either (muscular VSD). Surgical treatment depends on many variables, including which outflow tract is obstructed and the location and size of the VSD. Of note, in the TOF type of DORV, outcome is similar to TOF except that those with DORV are more likely to develop subaortic stenosis because of the baffling of systemic blood flow from the left ventricle to the Aorta. In the case of "doubly committed" VSD, the VSD must be baffled to one of the outflow tracts without causing obstruction to the other. If the VSD is more easily committed to the pulmonary artery, then an arterial switch operation must be performed as well. The VSD in some DORV subtypes is significantly remote from the conotruncal vessels and separation of the pulmonary and systemic circulations is not possible and the patient requires single ventricle palliation. Late postoperative sequelae are related to the type of repair performed.

Ebstein's Anomaly

Ebstein's anomaly is a rare malformation of the right ventricle and the tricuspid valve accounting for less than 1 % of all CHD. The septal and posterior leaflets of the tricuspid valve are displaced downward with abnormal attachments, often tethered, to the right ventricular wall. The anterior leaflet, while not displaced, is redundant and "sail-like". The atrialized right ventricle is the proximal inlet portion of the right ventricle that is above the inferiorly displaced functional tricuspid valve annulus, and the functional right ventricle is the remaining right ventricle that lies distal to the tricuspid valve inflow. The abnormal tricuspid valve is usually regurgitant but in rare cases may also be stenotic. This results in marked right atrial enlargement and cardiomegaly.

Hemodynamic abnormalities are related to the severity of tricuspid regurgitation, the size of the functional right ventricle, and the degree of right to left shunting at the atrial level and the pulmonary vascular resistance. The left ventricle may be affected due to bulging of the ventricular septum into the left ventricle. There is often severely diminished antegrade flow into the lungs with a large right to left shunt at the atrial level resulting in severe cyanosis. Ebstein's anomaly can be associated with atrial septal defect, pulmonary outflow tract obstruction and L-TGA. In addition, there is an increased incidence of Wolff-Parkinson-White syndrome in patients with Ebstein's anomaly. If there is severe tricuspid regurgitation in utero, massive cardiomegaly, secondary pulmonary hypoplasia, hydrops fetalis or a combination thereof may result [43].

Timing of Surgery

Ebstein's anomaly has a clinical spectrum that varies from severe cyanosis and circulatory collapse in the neonate to minimal or no symptoms in the child or adult [44]. Cyanosis is the most common presenting symptom in infancy. Cyanosis without other symptomatology may be managed conservatively because the hypoxemia may resolve as the pulmonary vascular resistance falls and the antegrade pulmonary blood flow increases. Neonates with severe tricuspid regurgitation often present at birth with cyanosis, metabolic acidosis, and circulatory collapse. If the heart is massively dilated from right atrial dilatation, pulmonary hypoplasia is common and the outcome is poor. The mortality rate is at least 20 % when a child with Ebstein's anomaly presents in the neonatal period [45]. In older patients, supraventricular tachyarrhythmias are a significant cause of morbidity. Surgery is reserved for the symptomatic patient with Ebstein's since repair of the valve is not always possible.

Method of Repair

In the neonate, an additional source of pulmonary blood flow (i.e. an aortopulmoanry shunt) may be required if cyanosis is significant. If the tricuspid regurgitation is severe, tricuspid valvuloplasty may be attempted. A variety of surgical techniques exist and most include some combination of tricuspid valvuloplasty, plication of the atrialized portion of the right ventricle, reduction atrioplasty of the right atrium and an anti-arrhythmia procedure such as the Maze procedure. The cone procedure mobilizes the anterior and posterior tricuspid valve leaflets from their aberrant ventricular attachment and the annulus. A cone is then created from the valve tissue as the free edge of the leaflets are rotated in a clockwise fashion and sutured to the septal leaflet attachment after plicating the atrialized right ventricle and creating a neo-annulus [46]. In some cases of repair, a bidirectional Glenn may be performed to decrease volume overload on the right ventricle. Occasionally, tricuspid valve repair is not possible and replacement is required.

Alternatively, the single ventricle pathway is utilized in patients with an inadequate right ventricle. A Starnes procedure involves closing the tricuspid valve orifice with a fenestrated patch limiting the regurgitation but allowing for right ventricular decompression, excising the atrial septum, plicating the atrialized portion of the right ventricle and inserting a systemic-to-pulmonary artery shunt. In older children and adults, right-to-left shunting at the atrial level can often be addressed by surgical or device closure of the ASD.

Follow-up

Mortality remains high for Ebstein's anomaly in association with severe tricuspid regurgitation and pulmonary hypoplasia; in some cases, referral for heart/lung transplant may be required. For those with less severe forms of the disease, specific postoperative problems include low cardiac output secondary to diminished forward flow from the right ventricle, residual tricuspid valve regurgitation and chronic atrial tachyarrhythmias [47]. Complete heart block may occur with tricuspid valve surgery. In long-term follow-up, the function of the tricuspid valve must be observed closely.

Other Lesions

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) and Other Coronary Artery Anomalies

Normally the right coronary artery (RCA) arises from the right sinus of Valsava and the left coronary artery (LCA) arises from the left sinus of Valsalva. The origins and courses of the coronaries can vary widely. There are particular rare anatomic variations of note, including ALCAPA. ALCAPA usually presents with symptoms of heart failure and coronary ischemia in the first several months of life after the pulmonary vascular resistance falls. In addition, infants with

ALCAPA often have hemodynamically significant mitral regurgitation due to ischemia or infarction of the papillary muscles.

Other rare coronary malformations include a coronary that courses between the two great vessels, a high take-off of a coronary artery, and coronary artery fistulae. The LCA coursing between the aorta and the main pulmonary artery may result in compression of the coronary and anginal symptoms, syncope or sudden death during extreme exercise. Unfortunately, patients are commonly completely asymptomatic and the initial presentation can be sudden death. If the origin of a coronary lies significantly above a sinus of Valsalva, an excessive take-off angle, a narrowing of the coronary ostium, or both, may result.

Coronary arterial fistualas can occur from either the RCA or LCA to any chamber of the heart, the coronary sinus, the vena cavae, the pulmonary artery, or the pulmonary veins. Although typically there is a single fistulous connection, there may be multiple ones. In patients with coronary fistulas, presentation in infancy is unusual. Late presentation, even into adulthood, is not uncommon. Typically, patients are asymptomatic and present with a murmur or, less commonly, with heart failure caused by a large left-to-right shunt from the fistula. Although there can be coronary insufficiency, it is rare for a patient to present with angina as an isolated symptom.

Timing of Surgery

ALCAPA repair is done at the time of diagnosis. Whether to repair the coronary artery that courses between the aorta and the main pulmonary artery is controversial in an asymptomatic patient because the postoperative risk of sudden death is not known. In general, these coronary anomalies are repaired at the time of diagnosis. Very small fistulous connections will sometimes close spontaneously, and conservative management may be employed. Small coronary arterial fistulas may enlarge over time, and careful follow-up is required. In asymptomatic patients with moderate to large fistulas, elective closure is usually indicated via interventional cardiac catheterization or surgery. Symptomatic patients should be addressed at the time of presentation.

Method of Repair

Surgical intervention for ALCAPA generally involves reimplantation of the coronary from the pulmonary artery to the aorta. If the coronary cannot be mobilized, an aortopulmonary window can be created with a baffle within the pulmonary artery, which channels the coronary blood flow to the aorta (i.e., the Takeuchi repair). The incision in the pulmonary artery is closed with a patch to compensate for the decrease in pulmonary artery size caused by the baffle. Before surgeons became facile at coronary reimplantation, the intervention for ALCAPA previously included ligation of the LCA in those with good collateral circulation from the RCA. This practice has been discontinued due to suboptimal outcomes [48]. If mitral regurgitation remains severe, mitral valvuloplasty or mitral valve replacement may be necessary.

In patients who have an anomalous course of a coronary artery between the aorta and the pulmonary artery, the method of repair depends upon the subtype. If the coronary ostium is normal, reimplantation in a manner similar to that described for ALCAPA may be possible. If the coronary ostium is slit-like or the coronary is intramural the ostium must be remodeled to prevent compression. Finally, in rare cases, bypass grafting may be necessary.

The manner in which coronary arterial fistulas are addressed is dependent upon location. In some patients, the fistula is very distal and the area of the myocardium supplied is insignificant. In such patients, the coronary artery may be ligated proximal to the fistula. In cases in which the fistula opens into an accessible area such as an atrium or the right ventricle, the opening may be sutured closed or patched from within the heart with an atriotomy (or a pulmonary arteriotomy if the connection is to the PA). In selected cases, the coronary arterial segment over the fistula may be opened longitudinally and the fistula oversewn from within the vessel. The overlying coronary artery is then carefully sutured closed. Coil embolization by cardiac catheterization is often possible to address these lesions, avoiding open-heart surgery altogether.

Follow-up

Coronary insufficiency is the primary concern after any intervention on the coronary arteries. In addition to echocardiography to assess ventricular function, nuclear studies are often indicated as a child grows to assess adequate myocardial perfusion. In some cases, cardiac catheterization is necessary to evaluate the coronary. In those with ALCAPA, long-term follow-up of mitral valve and ventricular function is required.

Vascular Rings and Slings

Vascular rings and slings are abnormalities of the aortic arch and arch vessels that may lead to compression of the trachea and/or esophagus. Presentation can vary widely. Complete vascular rings result from either a double aortic arch, which is the most common, or from a variety of vascular malformations which, together with the ligamentum arteriosum or PDA, form a ring around the trachea and esophagus and can results in compression of these structures. In the case of a double aortic arch, there is an anterior and leftward arch and a posterior rightward arch. Both branch from the ascending aorta then reconnect to constitute a single descending aorta. Typically, the right arch is dominant. The most common

vascular ring involving the ductus arteriosus is a right aortic arch with an aberrant left subclavian artery.

A vascular sling occurs when the left pulmonary artery arises posteriorly from the right pulmonary artery and courses posteriorly around the trachea and anterior to the esophagus. This anatomic arrangement can create a sling around the trachea at the level of the bifurcation of the mainstem bronchi and result in compression of the airway and tracheal stenosis.

Timing of Surgery

Complete vascular rings diagnosed in children of less than 6 months of age are typically associated with symptoms of airway obstruction and feeding intolerance and are corrected at the time of diagnosis. Very mild symptoms in older children may resolve with growth and elective division may be unnecessary in asymptomatic patients. Patients with left pulmonary artery slings who present with significant respiratory symptoms undergo repair.

Method of Repair

Double aortic arch is addressed by ligation and division of the non-dominant arch. The remainder of vascular rings are addressed by division of the ligamentum arteriosum or division of the PDA. Slings without tracheal stenosis can be addressed with a left thoracotomy. If performed through a sternotomy, repair of a sling includes division of the left pulmonary artery (LPA) at its origin and reimplantation into the main pulmonary artery anterior to the trachea. In all patients with significant tracheal stenosis, the trachea is divided and the stenotic segment either resected or managed by slide tracheoplasty. The LPA is mobilized and reanastomosed.

Follow-up

After successful correction of vascular rings, cardiology follow-up is not generally required. However, tracheomalacia may remain, and these patients may have long-term issues with airway obstruction. Follow-up after sling repair is required to assess respiratory insufficiency secondary to tracheal abnormalities and potentially narrowing of the pulmonary artery post-reimplantation.

Single Ventricle Repairs

Atresia of an atrioventricular or semi-lunar valve results in single-ventricle complexes (Table 23.1) that have complete mixing of the systemic and pulmonary venous circulations. Structural defects that are generally managed with a staged palliation include variations of single left ventricle (e.g., tricuspid atresia with normally related great arteries or transposition of the great arteries, double inlet left ventricle with normally related great arteries or transposition of the great arteries, malaligned atrioventricular canal with hypoplastic right ventricle, pulmonary atresia with intact ventricular septum) and variations of single right ventricle (e.g., hypoplastic left heart syndrome [HLHS], double outlet right ventricle with mitral atresia, malaligned atrioventricular canal with hypoplastic left ventricle, and heterotaxy syndromes).

Table 23.1 Single ventricle defects

Obstruction to pulmonary blood flow	Obstruction to systemic blood flow
Pulmonary atresia with intact ventricular septum	Hypoplastic left heart syndrome and variants
Tricuspid atresia with normally related great vessels	Mitral valve dysplasia with severe aortic stenosis
Right ventricular aorta with pulmonary atresia	Tricuspid atresia with d-transposition of the great arteries
Severe Ebstein malformation of tricuspid valve	Double inlet left ventricle with l-transposition of the great arteries
Unbalanced AV Canal to the left	Unbalanced AV Canal to the right

All of these lesions have complete mixing of the systemic and pulmonary venous circulations at the atrial and/or ventricular level. Thus, the pulmonary artery and the aortic oxygen saturations are equal, and the ventricular output (Total Q) is the sum of the pulmonary blood flow (Qp) and the systemic blood flow (Qs). This is contrary to normal physiology in which the pulmonary artery saturation is less than that of the aorta or transposition physiology in which the pulmonary artery saturation is greater than the aorta. The proportion of the ventricular output that goes to the pulmonary or the systemic vascular bed (Qp:Qs) is determined by the relative resistance to flow into both circuits. In most single ventricle lesions, one of the outflow tracts is obstructed. It is rare to have no outflow obstruction or to have obstruction to both circulations. With pulmonary outflow obstruction, pulmonary blood flow is determined by the degree of subvalvar or valvar pulmonary stenosis, the pulmonary vascular resistance and the size of the ductus arteriosus. Systemic blood flow in systemic outflow obstruction is determined by the severity of subaortic or aortic outflow obstruction, the systemic vascular resistance, and the size of the ductus arteriosus.

Children with single-ventricle anatomy generally undergo a palliative surgery in the neonatal period to achieve the following: (1) unobstructed systemic blood flow; (2) limited pulmonary blood flow to minimize the risk of pulmonary artery hypertension and ventricular volume overload; (3) non-distorted branch pulmonary arteries; (4) unobstructed pulmonary venous return; (5) unobstructed interatrial communication; and (6) a minimum of atrioventricular valve regurgitation. Essentially, the goal is to balance the pulmonary and systemic circulations. If there is insufficient pulmonary blood flow, the infant will be hypoxemic. If there is excessive pulmonary blood flow, it results in congestive heart failure.

The surgical palliation is variable depending on the single ventricle anatomy. Preoperative assessment for end-organ dysfunction, genetic syndromes, and additional congenital defects may be required, depending on the cardiac lesion identified and the preoperative condition of the patient.

Single Ventricle Surgical Procedures

Systemic to Pulmonary Artery Shunt

The modified Blalock-Taussig shunt is the palliative procedure most commonly used to augment pulmonary blood flow in single ventricle lesions with pulmonary outflow obstruction and cyanosis. A Gortex tube is placed from the innominate artery to the pulmonary artery. In situations in which the arch anatomy is abnormal, a central shunt from the ascending aorta to the pulmonary artery may be required. The classic Blalock-Taussig required sacrifice of the subclavian artery and therefore was abandoned. In the past, the Waterston and Potts shunts were used to provide pulmonary blood flow but they fell out of favor because they were associated with a high risk of pulmonary arterial hypertension and distortion of the pulmonary arteries.

Pulmonary Artery Banding

In children with a single ventricle in association with unrestricted pulmonary blood flow, congestive heart failure and eventual development of pulmonary vascular disease must be avoided. In patients with unrestricted pulmonary blood flow a pulmonary artery band is placed around the main pulmonary artery to limit pulmonary blood flow and lower pulmonary artery pressure. This procedure can be performed without cardiopulmonary bypass. The band must be placed in a position that will not distort either the pulmonary arteries or the pulmonary valve (the distortion of which would result in pulmonary insufficiency).

Pulmonary Artery-to-Aortic Anastamosis (Damus-Kaye-Stansel Procedure)

In children with single ventricle with subaortic stenosis or the potential for future sub-aortic stenosis, a Damus-Kaye-Stansel (DKS) palliation is performed in order to provide unobstructed flow from the ventricle to the systemic circulation [49]. The palliation involves an end-to-side anastomosis of the semilunar roots (main pulmonary artery to the aorta) to provide unobstructed systemic blood flow. Many of these patients will have arch obstruction and arch augmentation may be performed at the same time as the DKS, if necessary. Neo-aortic (i.e. native pulmonary) valve regurgitation is common after DKS repair, but it is rarely hemodynamically significant.

Norwood Procedure

The Norwood operation is a reconstructive procedure to palliate hearts with a functional single ventricle and aortic atresia or severe aortic hypoplasia, most commonly hypoplastic left heart syndrome [50]. The procedure involves augmentation of the aortic arch with amalgamation of the main pulmonary artery and the ascending aorta to provide unobstructed systemic blood flow and adequate coronary perfusion. An atrial septostomy is performed to assure adequate mixing and unobstructed pulmonary venous return, and a modified Blalock-Taussig shunt (MBTS) provides regulated pulmonary blood flow. The Norwood procedure continues to have one of the highest risks of mortality after congenital heart surgery.

Norwood with the Sano Modification

In light of the concern for adequate coronary perfusion, a modification of the Norwood has been developed, wherein a small (usually 5 mm) right ventricle-to-pulmonary artery valveless conduit is created obviating the need for a MBTS. With an RV to PA conduit the aortic diastolic blood pressure is higher and coronary perfusion is potentially improved.

Superior Cavopulmonary Connections and the Modified Fontan Operation

The eventual goal of surgical palliation for single-ventricle is to separate the systemic and pulmonary circulations. After the initial neonatal palliation, subsequent procedures are performed to transition the circulatory system to total cavopulmonary connections with passive pulmonary and pulsatile systemic blood flow. A superior cavopulmonary anastomosis is utilized to divert superior systemic venous return (SVC flow) directly into the pulmonary vascular bed, providing more stable and effective pulmonary blood flow and reducing the volume load on the single ventricle. Single-ventricle patients ultimately undergo a modified Fontan operation to complete the total cavopulmonary connection which allows inferior systemic vena return (inferior vena cava and hepatic venous flow) to enter the superior cavopulmonary connection.

Prior to staging with an interim superior cavopulmonary connection (SCPC), morbidity and mortality were high for single ventricle patients who transitioned directly from their initial palliative procedure to the Fontan operation. Common complications included severe ventricular dysfunction, large and prolonged pleural effusions, low cardiac output and tacharrhythmias. Surgical palliations, in which the single ventricle pumps to both the systemic and the pulmonary circulations, result in increased work load for the ventricle. This causes hypertrophy of the myocardium and increased ventricular mass. By staging to the modified Fontan with a SCPC, many of these hemodynamic alterations are less severe, with significantly lower morbidity and mortality at the time of the Fontan completion.

Superior Cavopulmonary Connections

After the initial palliative procedure, a SCPC (e.g., hemi-Fontan, bidirectional Glenn, and Kawashima procedure in the case of interrupted inferior vena cava with azygous continuation) is performed at 3–6 months of age as an interim procedure prior to the modified Fontan operation. This operation entails direct connection of the superior vena cava to the right pulmonary artery (i.e. a Glenn shunt or Kawashima procedure) or the creation of a baffle between the SVC and the right pulmonary artery along with placement of a dam between the SVC and right atrium (i.e. the Hemi-Fontan procedure) to promote SVC flow into the pulmonary artery. In the case in which there is a bilateral SVC, the left SVC is anastomosed to the left pulmonary artery as well (Bilateral bidirectional Glenn shunts). In order to be successful, the pulmonary vascular resistance must fall to a nearly normal level to allow passive blood flow into the pulmonary arteries [51, 52].

In general, the SCPC is well tolerated. Initially, many patients appear to be quite irritable with plethora of the upper half of the body likely secondary to the sudden increase in SVC filling pressure. This headache is treated with pain medication. Pleural effusions can occur in the postoperative period. The oxygen saturation is generally between 75 and 85 % after the SCPC.

Fontan Operation

In the modified Fontan operation, the inferior vena cava is connected to the SCPC. There are multiple technical modifications of the Fontan operation that have been developed over the past three decades [53]. In most centers, one or two of the methods are generally used, either the lateral tunnel Fontan (an intra-atrial baffle from the inferior to the superior vena cava) or the extra cardiac conduit (a GORE-TEX tube connection between the inferior vena cava and the SCPC) [54]. Many centers perform a fenestration in the Fontan baffle to help augment cardiac output and reduce pleural effusions during the postoperative period. The Fontan operation is generally performed at 2–4 years of age.

Risk factors for poor outcome after the modified Fontan operation include elevated pulmonary vascular resistance, pulmonary artery distortion, atrioventricular valve regurgitation, ventricular hypertrophy, and ventricular dysfunction. Improved patient selection, surgical technique and postoperative management have reduced the operative mortality to less than 5 % in most centers. The long-term outcomes, however, remain unknown [55, 56].

Patients who have had the Fontan operation require close follow-up for the remainder of their lives. Long-term follow-up issues include impaired neurodevelopmental outcome, altered cardiovascular mechanics, diminished exercise capacity, arrhythmias, somatic growth retardation, neo-aortic insufficiency, and thrombotic complications. Bradyarrhythmias and tachyarrhythmias are common after Fontan completion, and pacemaker placement or radiofrequency ablation may be required [57].

An idiopathic form of protein-losing enteropathy (PLE) develops in approximately 5–10 % of Fontan patients. This disease is characterized by chronic diarrhea with fecal protein loss, leading to loss of vascular oncotic pressure and the subsequent development of peripheral edema, ascites and pleural or pericardial effusions. Patients often become immunocomplromised from a loss of immunoglobulins. The etiology of PLE in Fontan patients remains unknown. Although there are a variety of treatments that achieved limited success in selected cases, many patients are refractory to treatment. Mortality is high, with only 50 % survival at 5 years from the time of initial diagnosis.

Common Lesions Receiving Single-Ventricle Palliation

A wide variety of complex lesions can result in common endpoint of the Fontan procedure. The three most common lesions are described below.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is a cardiac lesion with hypoplasia or atresia of the mitral and aortic valves in association with a left ventricular chamber that is either absent or too diminutive to support the systemic circulation. In the most severe cases, the aortic valve is atretic with a markedly hypoplastic ascending aorta (1 mm in diameter) and retrograde perfusion of the coronaries from the PDA. The Norwood and Sano procedures are the initial palliative surgeries for this lesion. Despite significant strides in technique, the incidence of sudden death after the Norwood procedure prior to a SCPC remains problematic. Residual hemodynamic abnormalities such as ventricular dysfunction, hemodynamically significant tricuspid regurgitation and distal arch obstruction portend for poor outcome. However, the etiology of sudden death often remains unclear. Abnormal heart rate variability, coronary insufficiency and low coronary flow reserve are likely to play a role. The long-term outcome for HLHS remains unknown as well. The oldest HLHS survivors at present are in their early 30s and had surgery in a different era than those undergoing intervention today. The durability of the right ventricle, the tricuspid valve, and the pulmonary valve in the systemic circuit remains in question.

HLHS patients who are at particularly high risk for poor outcome despite any intervention are those patients with

either an intact atrial septum or an inadequate atrial communication. Intact atrial septum in association with mitral atresia results in significant pulmonary venous obstruction with subsequent development of pulmonary arterial hypertension and pulmonary vascular obstructive disease. Even after the atrial-level obstruction is relieved, either by balloon septostomy or by surgical septectomy, the pulmonary arterial hypertension often remains, making the patient a poor candidate for Norwood procedure and later palliation. Marked thickening of the pulmonary veins with the appearance of multiple elastic laminae or so-called arterialization of the pulmonary veins has been noted. In some cases heart and lung transplantation is recommended.

Tricupsid Atresia

This is one of the earliest single ventricle lesions treated with surgical palliation. Absence of the tricuspid valve is often associated with right ventricular hypoplasia. An atrial communication is necessary for blood to exit the right atrium. Two-thirds of the patients with tricuspid atresia have a VSD with normally related great vessels. If the VSD is large, the pulmonary outflow may not be obstructed. However, if the VSD is small, pulmonary blood flow may be ductal dependent. Depending on the severity of obstruction at the level of the pulmonary outflow, a patient with tricuspid atresia may require a pulmonary artery band (to limit excessive pulmonary blood flow), a modified BT shunt (for insufficient pulmonary blood flow or pulmonary atresia) or no surgical intervention (for those with balanced pulmonary and systemic blood flow). One-third of patients with tricuspid atresia will also have transposition of the great arteries. In these patients there is hypoplasia of the aortic arch and a Norwood procedure is generally required.

Pulmonary Atresia with Intact Ventricular Septum

Pulmonary atresia with intact ventricular septum (PA/IVS) is defined as atresia of the pulmonary valve with no associated VSD and variable hypoplasia of the right ventricle and tricuspid valve. The main pulmonary artery is usually present and of normal size. Pulmonary blood flow is provided by a PDA. The tricuspid valve is generally stenotic, regurgitant, or both. Coronary-cameral fistulae are common in children with PA/IVS, especially in those who have small, hypertensive right ventricular cavities with a small tricuspid valve annulus [58]. In the most severe of cases, right ventricular-dependent coronary circulation exists when some of the myocardium is perfused only from the hypertensive right ventricle rather than anterograde from the aorta. The presence of right ventricular dependent coronary circulation has an important impact on possible surgical management strategies and is associated with a high mortality [59]. In these cases, decompression of the right ventricle (by establishing a communication with the pulmonary artery) results in severe coronary insufficiency and myocardial ischemia. Thus, almost all patients with PA/IVS undergo cardiac catheterization prior to surgical intervention to identify the coronary perfusion pattern.

Pulmonary blood flow is dependent upon left-to-right PDA flow and are managed using prostaglandins until a more reliable form of pulmonary blood flow is established. In those PA/IVS patients with an adequately sized tricuspid valve and right ventricle (and non-RV dependent coronary circulation), a transannular patch or right ventricle-to-pulmonary artery connection is performed to establish antegrade flow through the right heart. In some cases, a modified Blalock-Taussig shunt is also necessary to provide additional pulmonary blood flow. Right ventricular hypertrophy typically regresses over time with improved right ventricular compliance and increased right ventricular contribution to pulmonary blood flow. By 6 months to 1 year, the shunt is usually taken down surgically or coil occluded in the catheterization laboratory.

The treatment strategy is dependent upon size of the tricuspid valve annulus and the presence of right ventricular coronary circulation. In cases with a diminutive right ventricle, right ventricular dependent coronaries, or both, staged single ventricle repair is preferred, with a modified Blalock Taussig shunt as the initial procedure. Some centers prefer cardiac transplantation to staged palliation when coronary perfusion is right ventricle-dependent.

Conclusion

Surgery for CHD has changed remarkably over the last half century. The overwhelming majority of cardiac lesions can be addressed surgically with excellent outcomes due to pharmaceutical, catheter-based and surgical advances. Children with complex CHD are living into adulthood. Current challenges in the field of pediatric cardiac surgery include improving quality of life for survivors of complex CHD and developing smaller ventricular assist devices for neonates. Innovative treatment approaches are also in development including gene therapy, fetal cardiac intervention, creation of human tissue valves and prosthetic hearts. These exciting developments will only enhance the field of pediatric cardiac surgery and will enable us to better care for this complex surgical population.

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Palliative Procedures

24

Thomas B. Do, Mark A. Scheurer, and Andrew M. Atz

Abstract

Palliative procedures are performed on those patients who can never be completely repaired or who cannot be repaired safely at the time of their initial presentation whether it is due to complex anatomy, small birth weight, unfavorable hemodynamics, or a combination of these factors. Current techniques and procedures are varied and reflect the rapidly advancing technological achievements of designers and operators. This chapter will review indications for palliation, surgical palliations to either augment or limit pulmonary blood flow, catheter based palliations, as well as combined surgical and catheter based (hybrid) therapies.

Keywords

Congenital heart surgery • Hybrid procedure • Hypoplastic left heart syndrome • Pulmonary artery band • Aortopulmonary shunt

Palliate: to alleviate a symptom without curing the underlying medical condition
[From the past participle stem of *palliare* meaning "to cover or hide," from *pallium* meaning "a covering"].
(Merriam-Webster's Collegiate Dictionary, 11th edition)

History

Palliations are performed on those patients who can never be completely repaired or who cannot be repaired safely at the time of their initial presentation, whether it is due to complex anatomy, small birth weight, unfavorable hemodynamics, or a combination of these factors. Historically, all initial attempts to intervene in children with congenital heart disease were palliative in nature. The first surgical palliation for congenital heart disease was the now famous right subclavian artery to right pulmonary artery shunt ("classic" Blalock-Taussig shunt) performed by Blalock and Thomas in 1944 [1]. Rashkind and Miller's novel development of the catheter-based atrial septostomy in 1966 opened the door to a revolution in catheterization-based procedures that now often blur the distinction between cardiothoracic surgeon and interventional cardiologist [2]. As the field of pediatric cardiology has progressed, these invasive procedures are now not merely limited to the operating suite or the catheterization laboratory, because a balloon atrial septostomy can now be performed safely at the bedside [3]. Current techniques and procedures are varied and reflect the rapidly advancing technological achievements of designers and operators.

Indications for Palliation

Palliative procedures can be performed on those children in whom an eventual biventricular circulation is possible or those with single-ventricle physiology in whom other future procedures will be required. Initial complete repairs are sometimes unfeasible or unwise to attempt in the neonatal period due to

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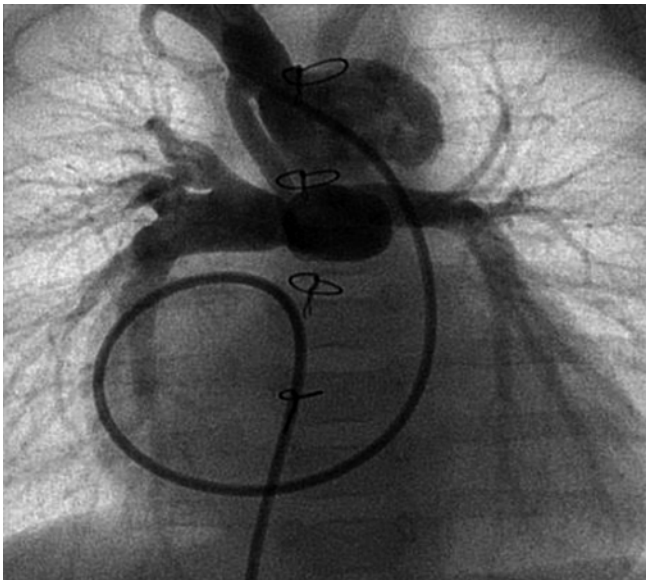

Fig. 24.1 Modified Blalock-Taussig shunt as part of a Norwood procedure for hypoplastic left heart syndrome. The shunt provides a controlled source of pulmonary blood flow

anatomic or co-morbid conditions. Stabilization of the physiology by augmenting pulmonary blood flow with a shunt or, conversely, limiting pulmonary blood flow with a pulmonary artery band can result in adequate somatic growth which may allow for eventual complete biventricular repair or a more favorable and stable single-ventricle physiologic state [4, 5].

Surgical Palliation to Supply Pulmonary Blood Flow

The most common palliative procedure to supply pulmonary blood flow is the systemic-to-pulmonary arterial shunt (Fig. 24.1). The "classic" Blalock-Taussig shunt, as originally described, anastomosed the subclavian artery directly to the ipsilateral branch pulmonary artery. This has been associated with long-term limb growth deficiency and diminished arm strength [6, 7]. Thus the "classic" Blalock-Taussig shunt has been replaced with the modified Blalock-Taussig shunt (Gore-Tex interposition graft between the innominate artery or subclavian artery and pulmonary artery, usually 3.5 or 4 mm in diameter) and this is now the most commonly performed procedure to secure adequate pulmonary blood flow in children with cyanotic congenital heart lesions [8, 9]. This method has been shown to supply a more predictable shunt volume than previous techniques, and its thrombosis rate is less than or comparable to other techniques [10, 11].

Both the Waterston (ascending aorta to right pulmonary artery) and Potts (descending aorta to left pulmonary artery) shunts have been largely abandoned, as they were associated with significant distortion of the branch pulmonary arteries and higher mortality because of either excessive or inadequate pulmonary blood flow [12–14]. However, complex aortic arch or pulmonary artery anatomy occasionally necessitate a consideration of the use of one of these direct central shunts, or more likely, the placement of a central Gore-Tex interposition graft between the ascending aorta and central pulmonary arteries [15, 16].

The right ventricle-to-pulmonary artery shunt has become increasingly more popular over the past decade as an alternative palliative technique to increase pulmonary blood flow [17]. It is usually accomplished by placement of a 5 mm nonvalved Gore-Tex conduit that allows for a direct connection between the right ventricle and main pulmonary artery via a right ventriculotomy. This becomes a more attractive option in patients such as those with abnormal aortic arch branching that would make placement of a modified Blalock-Taussig shunt more difficult. The right ventricle to pulmonary artery shunt also confers other potential advantages over the Blalock-Taussig shunt, particularly less diastolic runoff. The resultant higher diastolic pressure seen in the right ventricle to pulmonary artery shunt when compared to an aortopulmonary shunt results in improved coronary perfusion pressures and possibly improved perfusion of the somatic organs. In a large multicenter randomized control trial involving subjects having the Norwood procedure, the right ventricle-to-pulmonary artery shunt was shown to have greater transplant-free survival at 12 months than the modified Blalock-Taussig shunt [18–20].

Surgical Palliation to Control Pulmonary Blood Flow

Banding of some portion of the pulmonary artery has traditionally been employed to limit pulmonary blood flow in those patients whose anatomy is not amenable to complete initial repair and who are at risk for pulmonary overcirculation (Fig. 24.2) [21–24]. As complete repairs are more commonly performed in the neonatal period and infancy, these techniques are becoming less frequent. However, there remains a population of patients in whom initial complete repairs are unfeasible. This population includes a growing number of complex infants with multi-organ system dysfunction who are surviving because of aggressive intervention in the neonatal period. Banding procedures can sometimes be employed in these patients to allow for an evaluation of the extent and prognosis of their other organ system involvement while also allowing for interim somatic growth and greater hemodynamic stability. When performed, banding procedures are often done in infancy prior to the predictable drop in pulmonary arterial pressure by 2–3 months of age.

Several techniques of banding have evolved but they all can be fraught with complications. The band can migrate to the bifurcation of the branch pulmonary arteries or disrupt

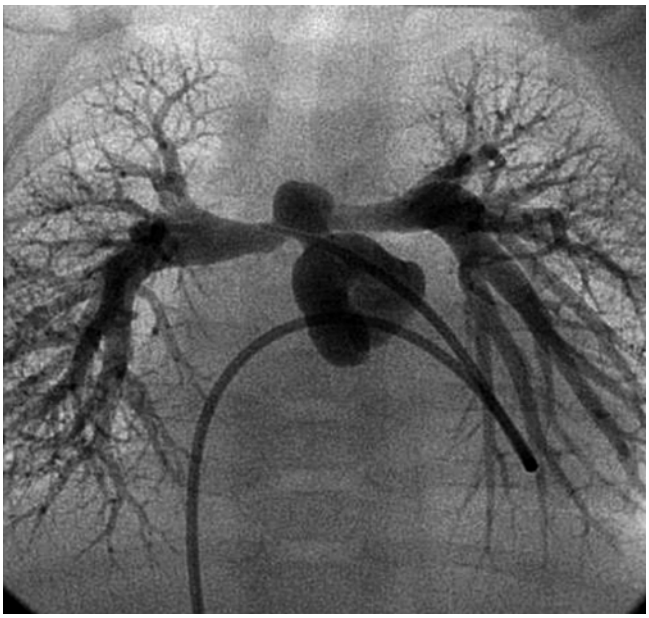

Fig. 24.2 Pulmonary artery band. This is placed distal to the pulmonary valve and proximal to the branch pulmonary arteries and limits excessive pulmonary blood flow

pulmonary valve architecture [25]. They have been known to occasionally loosen and can be difficult to manipulate during placement to allow for the optimal balance of pulmonary blood flow. Even the well-placed pulmonary artery band that does not disturb pulmonary valve function or encroach on the pulmonary artery branches may lead to unequal pulmonary arterial growth. It is therefore essential to evaluate the pulmonary artery architecture before proceeding with additional future surgeries.

There have been multiple attempts to develop surgically placed pulmonary arterial bands that can be later tightened or loosened externally depending on the clinical circumstances [26, 27]. However these methods have yet to reach wide-spread use. Recently, groups have developed the use of fenestrated patches placed within the right ventricular outflow tract or main pulmonary artery to limit pulmonary blood flow, although these techniques have the disadvantage of requiring cardiopulmonary bypass for placement [28]. Historically, surgical banding of the pulmonary arterial branches has been attempted in a few lesions. It was employed in early attempts to palliate children with truncus arteriosus but was thought to be a difficult technique to provide a predictable supply of pulmonary blood flow [29, 30].

Catheter-Based Palliative Procedures

Occasionally, a controlled source of blood flow is required in a cyanotic child with dynamic right ventricular outflow obstruction (such as in Tetralogy of Fallot) who is an unfavorable surgical candidate due to extreme prematurity or other co-morbid factors. Stents have been placed in the ductus arteriosus in some cyanotic patients with varying success [31–34]. If performed, care must be taken to not allow the stent to impede flow to the branch pulmonary arteries and that it should cover all aspects of ductal tissue, leaving no future substrate for coarctation of the aorta [35]. In selected patients, the right ventricular outflow tract can be balloon dilated or stented to allow for somatic growth and hopeful eventual complete repair [36].

Balloon atrial septostomy has been employed for many years as the initial palliative procedure in patients with transposition of the great arteries with an inadequate atrial level communication and no other significant source of mixing (multiple or large ventricular septal defects and/or patent ductus arteriosus) [37, 38]. Occasionally, this technique has been employed in children with an intact or restrictive atrial communication in hypoplastic left heart syndrome [39]. In these children, this procedure may also involve the placement of an atrial septal stent, as the septum can be thick and resistant to balloon disruption [40].

Staged Hybrid Palliation

Patients with single-ventricle physiology such as hypoplastic left heart syndrome who must undergo a three stage repair that ultimately end in the separation of their systemic venous return from the heart have significant short and long term morbidity and mortality. Given the tremendous physiologic and hemodynamic changes that transpire, the period with absolute greatest risk occurs after the first stage of palliation [41]. In an effort to minimize the physiologic stress a neonate encounters during the first stage of palliation where a major operation with significant cardiopulmonary bypass time and deep hypothermic circulatory arrest confers greater immediate morbidity and mortality, a new palliative technique was developed [42]. The hybrid stage I palliation allows time for the neonate to undergo somatic growth and continued development of their cardiac anatomy while setting the infant up for a stage II procedure that combines an arch reconstruction, pulmonary artery band removal, and bidirectional Glenn shunt with or without atrial septectomy at around 4–6 months of age when the surgical palliation may be better tolerated.

The hybrid palliation originally involved transcatheter stenting of the ductus arteriosus followed by bilateral branch pulmonary artery banding a few days later [43]. This approach has now been modified to its present day technique where the cardiothoracic surgeon first places bilateral pulmonary arterial bands then the ductal stent is positioned by an interventional cardiologist via a sheath in the main pulmonary artery (Fig. 24.3) [44–47]. A balloon atrial septostomy can

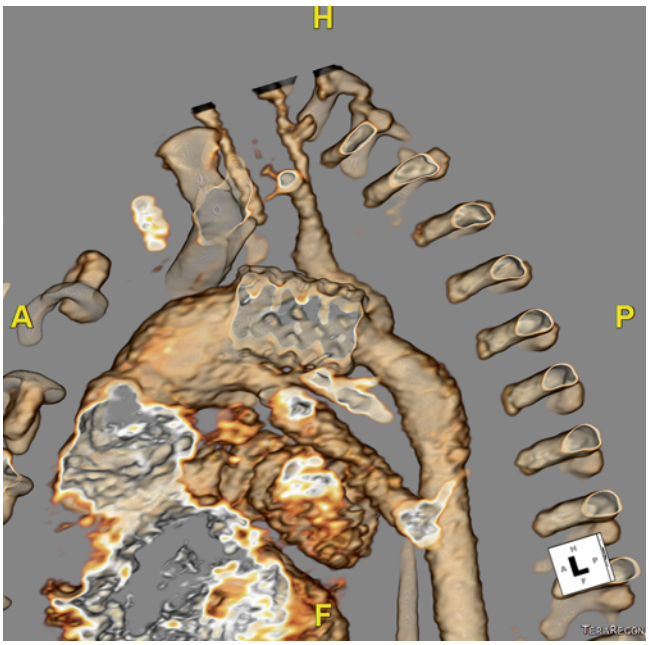

Fig. 24.3 CT angiogram illustrating the hybrid procedure for hypoplastic left heart syndrome. A stent is placed in the ductus arteriosus and bilateral bands are placed on each branch pulmonary artery. *A* anterior, *H* head, *P* posterior, *F* foot

also be performed for adequate atrial level mixing of blood if needed. The procedure is undertaken either in a specialized hybrid catheterization laboratory or in a modified operating room suite with adequate fluoroscopy equipment. No other procedure better illustrates the essential collaborative efforts and cooperation between cardiothoracic surgeons, interventional cardiologists, and cardiac intensive care staff required for the successful initial palliation of these patients with complex and technically challenging cardiac anatomy.

Some centers have exclusively employed the hybrid palliation in lieu of the traditional Norwood stage I operation. Most centers reserve this approach for their higher risk neonates such as those weighing less than 2.5 kg, those with severe atrioventricular valve regurgitation or right ventricular dysfunction, and co-morbid conditions making cardiopulmonary bypass more dangerous [48–51]. If the infant is unable to proceed towards the second stage palliation then the hybrid palliation still allows for a more favorable physiology and relative hemodynamic stability as the neonate awaits heart transplantation.

Intraoperative Assessment of Palliative Procedures

Experimental models have predicted that an ideal ratio of shunt size to body weight is 0.8–1.1 mm/kg. In this model, this ratio allows for predictable systemic to pulmonary blood flow and the ability to effectively manipulate the ratio with ventilatory and acid-base changes [52]. Reliable means do not exist in vivo, however, to evaluate the placement of a shunt that adheres to this ideal shunt to body weight ratio. Direct pressure measurement of the central pulmonary arteries and the ascending aorta provide a comparison of distal pulmonary arterial pressure to systemic pressure. Elevated pulmonary artery pressure in conjunction with low systemic diastolic pressure may indicate that the shunt is too large. Elevated pulmonary arterial pressure with a normal pulse pressure may indicate intrinsic pulmonary arterial hypertension and/or left atrial hypertension. By directly sampling mixed venous saturation in the venous cannula, obtaining central or peripheral arterial saturation, and assuming pulmonary venous saturation, the systemic-to-pulmonary shunt flow rate can be estimated intraoperatively. In the case of additional sources of pulmonary blood flow, such as a patent but diminutive right ventricular outflow tract, either the shunt or main pulmonary artery can be temporarily clamped and these measurements repeated to evaluate whether the additional source of pulmonary blood flow should be retained or modified.

The physiological effects of main pulmonary arterial banding can be similarly evaluated intraoperatively. The surgeon can quickly obtain direct pressure measurement of right ventricular pressure and pulmonary arterial pressure distal to the band. This allows for modification of the band, if necessary. The systemic-to-pulmonary pressure gradient can thus be determined intraoperatively. In the case of additional sources of pulmonary blood, flow can be determined as previously described. Intraoperative imaging with transesophageal echocardiogram also allows for both objective and subjective assessment of the operative procedure while still in the operative suite.

Post-procedure Management

Postoperative care of children with either a systemic-to-pulmonary arterial shunt or pulmonary artery band centers on the appraisal and maintenance of optimal systemic to pulmonary blood flow. Elevated systemic saturation together with evidence of poor peripheral perfusion and a metabolic acidosis signal an elevated pulmonary-to-systemic flow rate. In this case, efforts should be made to elevate pulmonary vascular resistance by minimizing inspired oxygen concentration and allowing for a mild respiratory acidosis. Additionally, a consideration of systemic afterload reduction with an agent such as milrinone should be made. Conversely, cyanosis and warm extremities signal diminished pulmonary blood flow. This can be caused by elevated pulmonary vascular resistance or partial shunt occlusion or kinking that can occur after chest closure. Regardless, efforts can be made to encourage pulmonary blood flow by employing measures to decrease pulmonary vascular resistance. These measures include

increasing inspired oxygen content, elevation of pH to 7.45–7.50 and PCO2 to 35 Torr through ventilatory manipulations and bicarbonate infusions, and considering the use of inhaled nitric oxide. In the shunted patient, if bedside echocardiographic imaging cannot unequivocally confirm shunt patency in the face of profound cyanosis, shunt occlusion with thrombosis should be strongly considered. Extracorporeal membrane oxygenation can be used as a bridge to surgical revision of a clotted and/or kinked shunt or in the case of intrinsic but presumed time-limited pulmonary arterial hypertension with an adequate, functioning shunt [53].

If effective pulmonary blood flow is diminished because of obstruction of the shunt at the aortic or pulmonary arterial anastomosis or kinking along its length, urgent surgical revision or catheter-based intervention is required. If thrombosis of a systemic-to-pulmonary arterial shunt is confirmed or highly suspected, a bolus of 100 U/kg of heparin should be given, and an infusion of tissue plasminogen activator or a similar fibrinolytic agent should be considered. There have been documented dramatic results of this therapy via systemic and directly guided tissue plasminogen activator administration [54–57]. If the patient has comorbidities that make systemic anticoagulation exceedingly dangerous (such as with an intraventricular hemorrhage), consideration of emergent surgical shunt revision with thrombectomy should be made.

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Peri-operative Care of the Child with Congenital Heart Disease

25

Alejandro A. Floh, Catherine D. Krawczeski, and Steven M. Schwartz

Abstract

This chapter provides readers with a general clinical framework to peri-operative patient care of children undergoing surgery for congenital heart disease, guiding them through pre-operative patient management, cardiopulmonary bypass and surgery, and post-operative recovery. Initial assessment with use of imaging (echocardiography, CT, MRI) and catheterization to delineate patient anatomy and physiology is vital for patient optimization. The intraoperative factors that can affect the post-operative recovery process are discussed including a practical review of the variations to cardiopulmonary bypass and its numerous physiologic effects. General post-operative issues including hemodynamics, patient monitoring, bleeding, sedation and analgesia, and distal organ disease are reviewed. Discussion of cardiac specific topics include issues related to cardiac function, low cardiac output syndrome, arrhythmias, pacing, the utilization of ECMO and ventricular assist, and factors affecting cardiopulmonary interaction are highlighted. Finally, readers are provided with lesion specific information that can affect post-operative recovery; including residual shunts, pulmonary hypertension, and single ventricle physiology. An emphasis is placed on anticipation of possible issues and early diagnosis to allow for quick and appropriate interventions.

Keywords

Child • Heart defects • Congenital • Cardiac Surgery • Cardiopulmonary bypass • Intensive Care Units • Pediatric • Post-operative care • Treatment outcome

Introduction

This chapter reviews the major issues involved in the intensive care management of children undergoing surgery for congenital heart disease (CHD). Optimization of care requires a thorough understanding of specific cardiac lesions, underlying cardiovascular physiology and surgical options; it is facilitated through appropriate surveillance, imaging and invasive monitoring.

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Pre-operative Management

Anatomy and Physiology

Fundamental to the care of the pediatric cardiac patient is a complete understanding of each patient's cardiac anatomy and physiology. This knowledge should guide medical stabilization, surgical decision-making, and peri-operative planning. Proper identification of single ventricle versus

two-ventricle physiology establishes the direction of management and forms the foundation of peri-operative care.

Neonates presenting with CHD may pose a unique diagnostic and therapeutic challenge to managing physicians. Detection of cardiac anomalies in fetal life has lessened the burden of undiagnosed infants, however undiagnosed patients, especially those with left-sided obstructive lesions, can present in a poor physiologic state and often in extremis. These individuals tend to require a period of stabilization prior to surgical intervention. Lesion-specific challenges also arise, such as balancing pulmonary and systemic blood flow in single ventricle anatomies. Physicians must also be cognizant of a limited number of lesions that cannot be stabilized medically and require urgent or emergent surgical or catheter-based intervention. These include, but are not limited to, obstructed total anomalous pulmonary venous connection, intact atrial septum in presence of transposition of great arteries or hypoplastic left heart syndrome, or critical aortic stenosis.

In post-operative planning, the patient with two ventricles undergoing a complete repair will generally emerge from the operating room with a normal "series" circulation. This allows application of the basic and well-understood principles of cardiovascular hemodynamics in the treatment of low cardiac output, hypotension or other common post-operative problems. Palliation for single ventricle lesions results in a more complex "parallel" circulation. The unique circulations that result from palliative surgical interventions for single ventricle lesions requires a special understanding of these circulations to effectively treat single ventricle specific post-operative problems and complications.

Pre-operative Clinical State

The clinical status of the patient in the pre-operative period should be carefully reviewed. This applies not only to the presence of congestive heart failure or cyanosis, but also to general pediatric issues such as failure-to-thrive, feeding difficulties, airway obstruction and other end-organ abnormalities. Knowledge of current or recent upper respiratory symptoms and febrile illnesses are extremely important, especially during the winter months when Respiratory Syncytial Virus (RSV) and Influenza are prevalent. Respiratory infections may significantly complicate post-operative convalescence and prolong mechanical ventilation and overall intensive care unit (ICU) and hospital length of stay [1]. The likelihood of anesthetic complications is increased when surgery and anesthesia are performed on a patient with an upper respiratory infection [2–4] and post-operative complications are more likely when cardiac surgery is performed in the presence of concurrent RSV infection [5]. The abnormal pulmonary mechanics associated with RSV infection may be particularly deleterious in patients in whom low pulmonary vascular resistance (PVR) is crucial, such as after cavopulmonary shunt or Fontan procedure, and in patients prone to dysfunction of the right ventricle (RV) or pulmonary hypertension. Optimal timing for cardiac surgery after RSV infection remains controversial, although most centers advocate a 6-week waiting period if cardiopulmonary bypass (CPB) is anticipated and if the patient condition allows.

The intensive care team should review all pre-operative cardiac testing. This will generally include a chest radiograph, echocardiogram, and electrocardiogram (ECG) and may include computerized tomography (CT), magnetic resonance imaging (MRI) or cardiac catheterization with angiography. These tests will provide insight into the patient's specific anatomic issues and pre-CPB myocardial and pulmonary function, and potential for residual anatomic lesions, low cardiac output, arrhythmia, and likelihood of pulmonary dysfunction during the post-operative period.

Pre-operative Cardiac Imaging and Hemodynamics

Echocardiography has emerged as the cornerstone imaging modality to evaluate segmental cardiac anatomy and delineate hemodynamics. In addition to assessment of ventricular function, ultrasound technology allows for interrogation of valve anatomy and function, obstruction to blood flow and intracardiac shunting. Further imaging with CT and/or MRI may be required for assessment of extra-cardiac vascular connections (e.g. coronary arteries, aortic arch and head and neck vessel anatomy, and pulmonary venous anatomy and connections), myocardial structure and function, and three-dimensional thoracic anatomic organization. The use of cardiac MRI, in particular, has increased substantially for pre-operative evaluation in attempts to minimize radiation exposure and complications. Several institutions have demonstrated effective pre-operative assessment of patients with hypoplastic left heart syndrome (HLHS), reaching equivalent outcomes compared to diagnostic catheterization, which remains the gold standard [6–8]. MRI imaging of right ventricular volumes and function also forms the foundation for timing of pulmonary valve replacement in patients who have undergone prior repair of tetralogy of Fallot [9, 10]. Although these advances have decreased the need for diagnostic cardiac catheterization in many children, some patients with congenital cardiac anomalies will require cardiac catheterization prior to surgery. This is usually done under three circumstances:

- The anatomic abnormalities are incompletely defined by the available non-invasive methods (echocardiography, CT or MRI).
- Hemodynamic evaluation is required prior to repair or further palliation.
- A therapeutic intervention is necessary.

When available, it is imperative that the physicians caring for the patient are familiar with the anatomic and hemodynamic information obtained by catheterization. This is especially important in those patients with a univentricular heart or whose anatomy results in single ventricle physiology who are undergoing staged palliation with cavopulmonary anastomoses (Glenn shunt, Hemi-Fontan, or modified Fontan procedure). Pre- or post-operative elevations in PVR may alter pulmonary blood flow and/or cardiac output in those patients. Resistance values must be interpreted with regard to pulmonary blood flow, since low-flow states may increase resistance measurements without actual vascular changes. Large inequities in blood flow distribution between the right and left lungs or significant aortopulmonary collateral vessels can also make resistance calculations inaccurate or misleading. If vasodilator testing has occurred during the catheterization, specific drug responses may help guide interventions to manipulate PVR in the post-operative period. Lastly, evidence of pulmonary venous desaturation during the catheterization may assist in managing those patients with unexpected hypoxemia after surgery.

It is important to recognize the limitations of invasive hemodynamic data, particularly with regard to diastolic ventricular function. The most common indicator of diastolic function is the ventricular end-diastolic pressure. Although a high ventricular end-diastolic pressure indicates dysfunction, a normal reading may not accurately predict postoperative performance, particularly in patients with single ventricle anatomy [11].

Previous Cardiothoracic Surgery

Outcomes after previous cardiothoracic operations should be noted. In particular, duration of mechanical ventilation, inotropic requirement, and any associated anesthetic complications should be reviewed. Prior unexpected episodes of hemodynamic instability, arrhythmias or sedation and pain control problems are of particular importance. Ventilator course and previous airway complications should also be noted. This pertains to patients at risk for vocal cord paralysis (such as those with previous aortic arch surgery), and to those who may have prior mechanical vocal cord damage. A history of airway compromise may alter the way that ventilator weaning and extubation are performed.

Intra-operative Course

Procedure/Post-operative Hemodynamics

In order to provide comprehensive management, the intensive care physician must be aware of the intraoperative course. Details regarding the surgical procedure and any complications must be communicated from the surgical team to the intensive care team. It has become routine in most centers to perform pre- and post-operative transesophageal echocardiography to evaluate the adequacy of intracardiac surgical repairs. It is imperative that the critical care team be aware of any residual lesions such as intracardiac shunts, valvar stenosis or insufficiency, and outflow obstruction. These lesions can have profound effects on the types of investigations and interventions that the ICU team considers for post-operative problems. Confirmation of the hemodynamic impact of lesions identified by transesophageal echocardiography may also be sought through invasive hemodynamic measurements in the operating room. Transvalvar or transpulmonary gradients can be measured directly, and oximetric studies to assess for residual shunts can also be performed. The results of any of these analyses should be conveyed to the ICU team. The surgical team should also communicate any the hemodynamic details of the patient's course since weaning from CPB. This includes heart rate and rhythm, relationships between filling pressures, blood pressure and, when applicable, arterial oxygen saturation and the amount of inotropic support. A formalized surgical team to ICU team "handoff" approach has been adopted by a number of surgical centers, optimizing communication during this transition in care teams.

Cardiopulmonary Bypass

Repair or palliation of most forms of CHD requires use of CPB for circulatory support. The CPB circuit replaces the function of both the heart and lungs during cardiac surgery. Venous drainage results from placement of a single cannula into the right atrium or from bi-caval cannulation, depending on the type of surgery and size of the patient. The aortic cannula is placed into the ascending aorta. The size of the cannulas and the flow rates on the pump depend on the size of the patient and the degree of hypothermia. Various reservoirs and filters are built into the circuit to protect the patient from air-bubbles, thrombi or acute changes in volume or hemodynamics.

Because of the need for reduced perfusion flow rates to minimize venous return to the heart during many types of congenital heart surgery, varying degrees of hypothermia are used during CPB. Hypothermia preserves organ function by decreasing cellular metabolism and preserving phosphate stores. As temperature is lowered, both basal and functional cellular metabolism is reduced, and the rate of ATP and phosphocreatine consumption is substantially decreased [12].

Three methods of CPB may be used, based on the required surgical conditions, patient size, type of operation and the potential physiologic impact on the patient:

- **Moderate hypothermic CPB (25–35 °C)** is the principle method of CPB used for older children and adolescents, and for the repair of less complex cardiac lesions such as atrial or ventricular septal defects. In these patients, the cannulas are less obtrusive and bi-caval cannulation allows for adequate drainage of the right atrium.
- **Deep hypothermic CPB (15–20 °C)** is usually reserved for neonates and infants who require complex cardiac repairs. It allows the surgeon to operate under conditions of low-flow CPB, which improves the operating conditions by providing a near bloodless field and generally allows the use of only a single atrial cannula. This results in better visualization of atrial anatomy and allows for repairs through a right atriotomy.
- **Deep hypothermic CPB with circulatory arrest** (DHCA) allows the surgeon to remove the atrial and, if necessary, the aortic cannulas and leaves a bloodless and cannula-free operative field. DHCA may be necessary when undertaking extensive aortic reconstructions, since there may not be any practical site in which to place the aortic cannula during this type of surgery. Clinical studies have indicated that the duration of safe circulatory arrest period to be approximately 45 min [13, 14]. However, mild neurologic deficits may be present in neonates after 30 min of DHCA, and impairment is more common if a VSD is present, suggesting that systemic air embolus may also contribute to the long-term neurodevelopmental deficits. Other organs generally tolerate circulatory arrest fairly well. Because of the neurologic consequences of DHCA however, many centers have adopted the technique of regional low-flow cerebral perfusion (RLFP) during aortic arch reconstruction in lieu of DHCA. RLFP provides low-flow perfusion to the brain either directly via the innominate artery or through the distal end of an innominate shunt. RLFP has been shown to decrease the period of cerebral ischemia by limiting decreases in cerebral blood volume and oxygen saturation and has been associated with better neurologic outcome in animals but data in children is less clear [15]. A randomized trial in infants undergoing CHD surgery demonstrated better outcomes with DHCA when compared to RLFP [16].

Support with CPB is geared toward maintaining adequate organ perfusion and systemic oxygen delivery. Flows are based on calculated rates for body surface area and adjusted based on mixed-venous saturation, acid-base status and lactic acid levels. Although complications from CPB are relatively rare, it is important for the intensive care physician to be aware of any intra-operative issues with the conduct of bypass and the general risks associated with its use.

Despite advances in perfusion technology, patients undergoing CPB uniformly develop a systemic inflammatory response resulting in tissue injury with transient myocardial dysfunction, which contributes to post-operative morbidity and mortality [17, 18]. This low cardiac output syndrome occurs approximately 6–12 h after separation from CPB and results in diminished myocardial contractility, increased afterload on the right and left ventricles due to increased PVR and systemic vascular resistance (SVR), and reduced myocardial preload due to third spacing from the systemic bypass-related inflammatory response [18]. The use of CPB has been associated with upregulation or activation of numerous inflammatory cytokines including tumor necrosis factor (TNF) and interleukins 6, 8 and 10, most likely due to the extensive contact of blood with artificial surfaces and possibly the non-pulsatile nature of CPB flow [17, 19]. There is also evidence of a stress response, with increases in many stress-related hormones. The response to CPB is similar to the systemic inflammatory response that occurs in sepsis, with a major difference being the inherent time-limited nature of bypass-related inflammatory injury. One important consequence of bypass-related inflammatory injury is pulmonary endothelial dysfunction that increases the endothelin/nitric oxide ratio present in the pulmonary vasculature and leads to post-operative pulmonary hypertension [20]. This occurs because the pulmonary endothelium is deprived of its major nutritive source of blood flow during CPB as the lungs are bypassed. Similar aberrations of systemic endothelial function resulting in inappropriate systemic vasoconstriction are thought to occur after DHCA [18].

Other clinical manifestations of systemic inflammation can include capillary leak with third space loss of fluids, alterations in SVR and transiently diminished renal function [19, 21]. The time course of CPB-related injury generally peaks at 12–18 h following CPB, so that it is reasonable to expect some clinical worsening during this time frame, although in practice it is often relatively minor. However, for patients with particular risk factors that might be exacerbated by CPB such as pre-operative elevations in PVR or poor myocardial function, the initial post-operative period is when these problems are likely to manifest.

Cardioplegia and Myocardial Protection

Most repairs of CHD require the surgeon to open the heart so as to repair septal defects, construct baffles or replace or repair valves. Such procedures generally require the use of cardioplegia. The goal of cardioplegia is not only to arrest the heart in a relaxed state, but also to preserve the myocardium during this period of ischemia. Cardioplegic solution contains many additives and the composition varies from surgeon to surgeon. Many of the additives provide substrate for myocardial energy metabolism, and others are thought to enhance preservation and minimize inflammation. Cardioplegia is usually administered cold (4–8 °C) and is often mixed with oxygenated blood. Topical hypothermia

(ice slush) may also be used, but has been associated with an increase in phrenic nerve injury [22]. Cardioplegia is a high potassium solution that is usually administered into the aortic root (i.e. antegrade) after cross-clamping the aorta above the coronary arteries. The cardioplegic solution perfuses the coronary circulation and causes the myocardium to arrest in diastole. Repeated doses are given throughout the case to ensure myocardial preservation. Cardioplegic solution can also be administered in a retrograde fashion via the coronary sinus when the coronaries have been removed from the aorta (arterial switch operation) or when there is severe aortic insufficiency, which can cause run-off of the solution into the ventricle.

Despite the effort to maximize myocardial preservation during cardioplegia, its use is associated with an increased likelihood of myocardial dysfunction following surgery. The longer the period of aortic cross-clamp, the more damage the myocardium is likely to sustain. Similar to bypass-related injury, myocardial ischemia-reperfusion injury involves activation of inflammatory mediators within the myocardium and has also been associated with protease activation, degradation of contractile proteins and myocyte apoptosis [23–25]. The RV is particularly vulnerable to inadequate myocardial protection. The anterior position, of the RV makes it more difficult to consistently achieve adequate hypothermia due to passive rewarming from the ambient air [26]. Furthermore, in the presence of right ventricular hypertrophy or retrograde cardioplegia, perfusion may be less adequate [27, 28].

Despite the transient nature of post-operative myocardial injury, there may be some element of permanent damage, particularly after very long procedures, multiple episodes of ischemia and reperfusion or when adequate myocardial protection is difficult such as with aortic insufficiency. Nevertheless, the benefits of repairing residual lesions often tip the risk/benefit ratio in favor of returning to CPB to repair residual lesions identified by post-operative transesophageal echocardiography. Strategies to prevent myocardial injury include the use of pre- and intra-operative high-dose steroids and modified ultrafiltration [29–31].

Modified Ultrafiltration

CPB results in a significant inflammatory response with increased capillary permeability and total body water. In addition, the relatively small blood volume of children relative to the priming volume of the CPB circuit causes significant hemodilution. Hemofiltration is a process that uses convection to remove water and low molecular weight substances from plasma under a hydrostatic pressure gradient. This process effectively removes excess body water and several major inflammatory mediators, and results in hemoconcentration after termination of CPB. It has been shown to improve hemodynamics, cardiac contractility and oxygenation, and reduce post-operative blood loss and duration of mechanical ventilation [32, 33]. The process currently used is called modified ultrafiltration (MUF), and occurs after separation from CPB. The venous cannula is clamped or removed, and the arterial cannula is used to circulate blood from the patient through a hemofilter. The gas exchanger on the main CPB circuit is excluded from the system and blood is then directed slowly through the hemofilter to a small vent inserted into the right atrium. During MUF, all hemodynamic parameters are carefully monitored and the hematocrit is measured at regular intervals.

Basic Principles of Post-operative Care

General Principles

The goal of post-operative care in all cases is optimum oxygen delivery and perfusion at an acceptable blood pressure and, in the case of cyanotic patients, saturation. It is essential to realize that blood pressure is not the same as perfusion, although it is often used as a marker for adequacy of cardiac output. Cardiac output is the product of stroke volume and heart rate, whereas blood pressure is a product of cardiac output and SVR. Furthermore, increases in SVR represent an increase in afterload on the systemic ventricle, which may diminish cardiac contractility and cardiac output. Thus, blood pressure that is maintained by an increase in SVR at the expense of cardiac contractility and cardiac output may represent decreased tissue oxygen delivery compared to a low resistance/high cardiac output state. Nevertheless, a certain minimum (age-dependent) blood pressure is necessary to maintain adequate organ perfusion.

As soon as practically feasible, the post-operative patient should receive a full examination. This includes the obvious assessment of hemodynamic stability and adequacy of tissue perfusion, as well as the presence of any murmurs, rubs or gallops, air entry into the lung fields and degree of hepatomegaly. The patient may still be under the systemic effects of general anesthesia, so a full neurological examination may not be possible. However, the fontanel (if still present) and pupil responses should be checked. A more complete neurologic examination should be completed when appropriate. The sites of in-dwelling catheters, wires and monitoring devices should be noted and carefully examined for position and function. This includes peripheral and central intravenous lines, arterial catheters, atrial lines, endotracheal, nasogastric, mediastinal and pleural tubes, pacing wires and urinary catheters. A chest radiograph is usually obtained upon admission to the ICU, and should be checked in a timely fashion noting positions of the various in-dwelling

catheters and tubes, heart size, presence of pleural effusions and pneumothorax.

Hemorrhage and Clotting

The volume of mediastinal drainage should decrease rapidly hour-to-hour during the first 6 h, and the nature of the drainage should change from frankly bloody to serosanguinous and ultimately serous during the first 18–24 h. Factors that may promote persistent hemorrhage include preoperative cyanosis with polycythemia, reoperations and multiple suture lines. Once a mainstay of anti-fibrinolytic therapy, aprotinin was withdrawn from market following the Blood Conservation Using Anti-fibrinolytics in a Randomized Trial (BART) study which demonstrated a mortality risk [34]. Tranexamic acid and epsilon aminocaproic acid, which are anti-proteolytic lysine analogues, continue in use to minimize post-operative hemorrhage. Bloody drainage that continues at a volume greater than 10 ml/kg over the first 2 h or 5 ml/kg thereafter should raise concern, and if it continues despite blood product and clotting factor replacement, re-exploration may be indicated. Conversely, if the mediastinal drainage suddenly ceases and clots are noted within the tube, the possibility of contained intrathoracic hemorrhage and cardiac tamponade should be entertained. An activated clotting time (ACT) is measured at the completion of bypass. This is a moderately sensitive screening test for deficiencies in the intrinsic and common pathways of the clotting cascade. This tests for potentially all types of clotting factor deficiencies with the exception of factor VII of the extrinsic cascade, but is practically used to assess the persistent post-bypass effects of circulating heparin. Normal values vary between 120 and 150 s. Protamine is used to reverse heparin effects and is given in the operating room in a dose based on the amount of heparin given before and during CBP. For the patient who continues to bleed in the intensive care unit, a second dose of protamine is often given. This dose should be less than the initial dose since overdoses of protamine can actually promote bleeding. It is also important to realize that the hypothermia associated with CPB inactivates platelets. Like protamine, platelets are usually given at the conclusion of CPB, but it is common for patients to have a normal platelet count with diminished platelet function. It is therefore often helpful to repeat the platelet transfusion in the ICU for the patient with persistent bleeding. If the prothrombin and partial thromboplastin times (PT and PTT) are elevated in the bleeding patient, treatment with cryoprecipitate (2 units/10 kg body weight) or fresh frozen plasma (10 ml/kg) is indicated. Finally, in cases of significant bleeding recombinant Factor VIIa has been shown to help reduce post-operative bleeding, however it is associated with an increased risk of thromboembolic phenomena [35–37].

Acid-Base Status

Acid-base status is monitored frequently following cardiac surgery. It gives information about oxygenation, ventilation and tissue perfusion. Although in most patients, the goal is to maintain a normal acid-base status, many patients will tolerate a mild respiratory acidosis during an attempt at early weaning from mechanical ventilation, and those with a bidirectional superior cavopulmonary anastomosis (bidirectional Glenn shunt) may actually benefit from a respiratory acidosis because of the associated increase in cerebral and thus pulmonary blood flow. Alternatively, when elevated PVR is a concern, it may be desirable to maintain a mild to moderate respiratory alkalosis to minimize PVR.

The PaO_2 measurement on the arterial blood gas may be particularly helpful in cyanotic patients. Since pulse oximetry is not as accurate at low oxygen tension, the direct measurement of arterial oxygen levels can help the clinician evaluate the adequacy of pulmonary blood flow. As a general rule, a PaO_2 <30 is not well tolerated for prolonged periods of time. When pulmonary blood flow reaches a critically low level as reflected by a PaO_2 <30, CO_2 removal is often hampered as well, leading to respiratory acidosis, increase in PVR and metabolic acidosis from impaired oxygen delivery. This is an unstable situation and must be corrected in a timely fashion by either medical means to improve pulmonary blood flow, mechanical support or, when appropriate, re-operation.

In the post-operative patient, an anion-gap metabolic acidosis should be considered an indication of low cardiac output and inadequate tissue perfusion until proven otherwise. Common causes of low cardiac output immediately following surgery include arrhythmia, tamponade, hypovolemia, myocardial dysfunction, pulmonary hypertension and residual anatomic lesions. Many of these causes can be ruled out with a thorough knowledge of the pre-operative and intraoperative course including the results of the transesophageal echocardiogram as well as a thorough examination of the patient, ECG and assessment of information from indwelling hemodynamic monitoring lines.

Blood lactate levels are often used as a marker of diminished systemic perfusion and as a predictor of outcome after heart surgery. Elevated or rising lactate levels in the early post-operative period indicate inadequate oxygen delivery and suggest an increased risk of morbidity and mortality [38–40]. Furthermore, progressive increases in serum lactate levels may enhance the predictive value of monitoring lactate levels post-operatively [41]. Unfortunately, blood lactate levels may become elevated only with significant circulatory dysfunction, after the anaerobic threshold has been reached, below the point when oxygen consumption becomes dependent on oxygen delivery [42]. In addition, elevated blood lactate might not reflect the current state of well-being but rather relate to prior (pre- or intraoperative) periods of diminished

tissue perfusion with end-organ injury and inability to metabolize existing lactate.

Hemodynamic Assessment

Almost all patients who have undergone surgery for CHD will have arterial and central venous catheters. Those who have had more complex procedures will also have transthoracic intracardiac lines to monitor atrial pressure (right, left or common) or pulmonary artery pressure. In some cases these lines may be placed so that the tip allows sampling of blood from a particular site such as the superior vena cava or they may be capable of providing continuous oximetric data. The data gathered from such monitoring lines can be extremely helpful for assessing ventricular function or volume status when determining the cause of post-operative problems such as hypotension, poor perfusion or low urine output. High left-sided or systemic filling pressures suggest the possibility of systemic ventricular dysfunction, residual left-to-right shunt or valve dysfunction, depending on the particular anatomy and repair. High left-sided filling pressures will also lead to pulmonary venous hypertension and thereby increase pulmonary artery pressure, which can be problematic after cavopulmonary anastamoses (Glenn shunt or Fontan operation). High right-sided filling pressures are suggestive of right ventricular diastolic dysfunction often seen after repair of lesions associated with significant right ventricular hypertrophy such as tetralogy of Fallot. Other causes of high right-sided filling pressures include severe pulmonary stenosis or insufficiency, tricuspid stenosis (rare) and pulmonary hypertension. It is important to realize that right-sided filling pressures are only indirectly reflective of pulmonary artery pressure. Elevated filling pressures in both atria indicate biventricular dysfunction either due to primary myocardial dysfunction or because of failure of one ventricle with subsequent influence on the other via septal position and ventricular-ventricular interactions. Elevated filling pressures in both atria also raise the possibility of cardiac tamponade, although tamponade can occur in the absence of elevated filling pressures if there is a localized collection of blood or fluid that impedes cardiac filling.

Careful analysis of waveforms may also provide insight into myocardial performance, the status of the atrioventricular valves, or cardiac rhythm. The atrial tracing may have canon a-waves, which occur when the atria contract against a closed atrioventricular valve. This indicates lack of atrioventricular synchrony and can occur with severe first-degree atrioventricular heart block when there is underlying sinus tachycardia, second or third degree heart block, junctional rhythms or atrial flutter. Large a-waves may also occur in the presence of atrioventricular valvar stenosis. Exaggerated v-waves can indicate atrioventricular valve insufficiency.

Oximetric Assessment

Mixed-venous oxygen saturation (SvO_2) and the arterial-venous oxygen saturation difference [$SaO_2 - SvO_2$] are often used to assess cardiac output and oxygen delivery. In patients with intracardiac shunts, superior vena cava (SVC) saturation is the best estimate of mixed-venous oxygen saturation [43], and many investigators have advocated continuous or intermittent monitoring of SVC saturation in post-operative patients [44–47]. Low SvO_2 and elevated arterial-venous oxygen saturation difference are sensitive predictors of low systemic blood flow and inadequate oxygen delivery; an arterial-venous oxygen saturation difference greater than 40 suggests significant impairment in cardiac output and may be associated with inadequate tissue oxygen delivery [48]. Monitoring of SVC saturation is particularly useful after Norwood palliation, since systemic output in these patients depends on both myocardial performance and the balance of systemic and pulmonary blood flow. In patients after Norwood procedure, anaerobic metabolism and metabolic acidosis are likely when the absolute SvO_2 falls below 30 % [49].

Measurement of cerebral oxygen saturation by continuous near-infrared spectroscopy (NIRS), a representation of regional cerebral oxygenation index (rSO_2) or tissue oxygenation index (TOI), has been used to estimate the balance between cerebral oxygen delivery and consumption. Peri-operative use continues to expand and is currently being employed for monitoring of single and biventricular physiology to assess adequacy of cerebral oxygen delivery and extrapolated to reflect overall cardiac output [50, 51]. Several studies have demonstrated a strong correlation between these indices and SvO_2 [52], however these findings are not universal [53–55]. Low NIRS (<45) for prolonged periods have demonstrated anatomic correlation of cerebral ischemia [56]. The role of splanchnic NIRS is more controversial with conflicting data regarding its ability to reflect hemodynamic status [55].

Post-operative Intubation and Ventilation

Early extubation (variably defined as less than 6–24 h post-operatively) of low risk cardiac surgical patients has been shown to be possible and safe in infants and children. Extubated patients have been shown to have shorter ICU and hospital stays, and less morbidity and mortality; however larger studies are needed. To facilitate efficient patient flow, system changes including anesthetic management, post-operative analgesia, and monitoring protocols have been proposed.

For patients who remain ventilated, mechanical ventilatory support is usually fairly straightforward following surgery for CHD. Most patients have healthy lungs, so the

purpose of mechanical ventilation is to ensure airway protection and adequate gas exchange until the heart and lungs have recovered sufficiently to undertake these activities without assistance. Either volume or pressure ventilation is generally acceptable or support can be rapidly weaned as the patient resumes wakefulness. Respiratory distress that develops after extubation can be due to several issues including congestive heart failure secondary to residual left-to-right shunts or inadequate Qs from unbalanced Qp:Qs or myocardial dysfunction, phrenic nerve injury with hemi-diaphragm paresis, pleural effusion or pneumothorax or chylothorax, airway obstruction due to acquired or congenital anomalies (e.g. vocal cord paresis following aortic arch repair), or pulmonary parenchymal disease. Clinical examination of respiratory pattern, auscultation and a chest radiograph before reintubation can help to establish the correct diagnosis or guide further investigation.

It is imperative to consider cardiopulmonary interactions when evaluating the form and mode of ventilation. Mechanical ventilatory support can have deleterious cardiac effects or, in some cases, it can be an adjunct to cardiovascular therapy. Manipulation of $PaCO_2$ has long been a staple of management for patients with increased PVR and pulmonary hypertension, and as mentioned previously, high $PaCO_2$ can be used to increase cerebral and thus pulmonary blood flow following bidirectional Glenn [57, 58]. Patients with low cardiac output, myocardial dysfunction, residual left-to-right shunts and pulmonary edema benefit from positive pressure ventilation because it reduces systemic ventricular afterload and can help counteract hydrostatic forces that promote pulmonary blood flow and pulmonary edema. It is important to remember that the lowest PVR occurs when end-expiratory lung volumes coincide with functional residual capacity and that high airway pressures in the presence of healthy pulmonary parenchyma are transmitted to the pulmonary vasculature and increase right (pulmonary) ventricular afterload. In these situations mechanical ventilation can be prolonged, either electively or because maintenance of adequate gas exchange cannot otherwise be accomplished. Nevertheless, several patient populations exist in whom raised intrathoracic pressures are not desirable. These include children with restrictive right ventricular physiology, right ventricular dysfunction or failure, and palliated single ventricle physiology (bidirectional and total cavopulmonary shunts) [59–61]. In the absence of pulmonary parenchymal disease, improved hemodynamics can be seen with lower (or negative) pulmonary pressures and preferably early extubation [60].

Arrhythmias

It is essential to determine the cardiac rhythm when the patient returns from the operating room. A multi-lead surface ECG should be performed as soon as possible and should be compared to the pre-operative ECG. All caregivers must remain alert to the possibility of changes in rhythm. In the early post-operative period, maintenance of atrioventricular synchrony is a vital component of maximizing cardiac output and oxygen delivery. In addition to the ECG, other tools that can be used to determine the cardiac rhythm include the bedside monitor and pacing wires, particularly the atrial wires. The bedside monitor is the most readily accessible way to examine cardiac rhythm, but may provide the least information. It is reasonably useful for QRS analysis, but p-waves may be hard to identify, particularly at faster rates. When the p-wave is not clearly seen or the rhythm is not clear after examination of the surface ECG, an atrial wire recording can be used. This is done by using one or more of temporary atrial pacing wires as a limb lead and allows for the amplified p-wave to be recorded directly from the surface of the heart.

Common arrhythmias following congenital heart surgery and their usual modes of treatment are as follows:

- **Ectopic Atrial Tachycardia** is due to abnormal automaticity at a specific site within the atria. It occurs as a narrow complex tachycardia with a 1:1 VA relationship and may be incessant. Although p-waves are usually identifiable, careful comparison with the pre-operative ECG should identify differences in p wave morphology and axis, although these differences may be subtle, particularly if the ectopic focus originates in the right atrium. Atrial tachycardia typically has a "warm-up" period but is characterized by little short-term or beat-to-beat variability, distinguishing it from sinus tachycardia. Prolonged atrial tachycardia may lead to cardiac dysfunction. Adenosine, cardioversion, and overdrive pacing do not terminate the tachycardia. Conservative management includes correcting acid-base and electrolyte disturbances, reducing the patient's catecholaminergic milieu, cooling, and giving a sedative and/or muscle relaxant to slow the tachycardia rate and improve hemodynamics. Tachycardia may also be limited by ensuring that wires and catheters are free from the atrial cavity. Nevertheless, treatment is generally with anti-arrhythmic agents; amiodarone is often considered the drug of choice, often in combination with β-blockade or class I anti-arrhythmic agents. Digoxin has minimal efficacy, except as a means to slow down the atrioventricular (AV) node response in the case of tachycardia and inadequate cardiac output. Amiodarone rather than β-blockade would be the choice of drug in setting of myocardial dysfunction. Finally, radiofrequency ablation is an option for tachycardia refractory to medical therapy.
- **Atrial Flutter** is a re-entrant tachycardia within the atrium. It may have 2:1 or 3:1 AV conduction, and is generally associated with a narrow QRS complex. This

rhythm disturbance is more common in patients with severe right atrial enlargement or after extensive atrial surgery (e.g. Ebstein's anomaly, Mustard, Senning). The typical atrial "sawtooth" flutter waves may be unmasked during treatment with adenosine, a feature that can be helpful in making the diagnosis. It is treated with either rapid atrial pacing at a rate greater than the atrial rate (overdrive pacing), or with synchronized direct current cardioversion (0.5–2 J/kg). Recurrent episodes may require treatment with amiodarone or other anti-arrhythmic agents.

- **Junctional Ectopic Tachycardia** (**JET**) is a common tachyarrhythmia that usually occurs in the first 48 h after surgery, seen in younger patients, and is associated with ventricular septal defect (VSD) closure, arterial switch operation, and the Norwood procedure [62]. It is generally poorly tolerated, especially in patients with unstable hemodynamics. A surface ECG or atrial wire study is required for diagnosis. Narrow complex tachycardia with AV dissociation with an R-R interval (QRS to QRS interval) that is shorter than the P-P interval (p-wave to p-wave interval) is pathopneumonic for JET; retrograde 1:1 VA conduction is not uncommon. The loss of AV synchrony and shorter ventricular depolarization cycle length at higher rates is the cause of hemodynamic impairment. When JET occurs there is no coordinated atrial contraction filling the ventricle at the end of ventricular diastole at a time when there is already diminished passive diastolic filling in the ventricle due to the faster ventricular rate. Slower junctional rhythms or junctional bradycardia, while not technically JET, may also lead to suboptimal hemodynamics and should be treated. Early recognition of JET and other arrhythmias may be aided by careful surveillance of atrial pressure waveforms; loss of the distinct a and v waves indicating loss of AV synchrony is often the first indication of arrhythmia. Patients with JET will often manifest large a-waves called "Cannon a-waves". Treatment of JET is directed toward rate control and the re-establishment of AV synchrony. Conservative management includes reducing endogenous and exogenous catecholaminergic state of the patient. This is most easily accomplished by reducing inotropic support if possible [62], sedation and/or muscle relaxation and temperature control (active cooling if necessary). Pacing, either atrial (if AV conduction is preserved) or AV sequential is then employed. If the underlying junctional rate remains too fast to allow pacing, the goal of pharmacologic therapy is to provide further rate control to allow institution of pacing. Although intravenous amiodarone generally is considered the drug of choice [63], induction of hypothermia and procainamide also have been shown to be effective [64]. In extreme cases, mechanical support may be necessary for refractory tachycardia. Finally, since JET is often a marker of residual hemodynamic problems, its appearance should lead to a thorough evaluation for residual lesions.
- **Heart Block** occurs when there is a prolonged PR interval (1st Degree), progressive prolongation of the PR interval until AV conduction is lost (2nd Degree Type I/Wenkebach), AV conduction that occurs in a fixed ratio other than 1:1 (2nd Degree Type II) or complete loss of AV conduction (3rd Degree/Complete Heart Block). Heart block may occur after any surgery around the AV node including operations involving VSD repair, mitral valve replacement or enlargement of the left ventricular outflow tract (e.g. Konno procedure or Rastelli operation). Patients with L-looped hearts or left-handed ventricular topology are at increased risk for heart block. First degree heart block and 2nd Degree Type I heart block rarely causes clinical problems, although very prolonged AV conduction in the face of tachycardia can have much the same effects as JET, particularly in the immediate post-operative period. Second Degree Type II heart block and 3rd Degree heart block require treatment with temporary pacing. Atrial pacing alone is not sufficient for high grade 2nd Degree and 3rd Degree heart block and AV sequential pacing is recommended. When this is not possible, ventricular pacing will prevent ventricular bradycardia (inadequate ventricular escape rhythm) and inadequate cardiac output and oxygen delivery to the tissues. When complete heart block is new following surgery, conduction may return as myocardial edema and inflammation resolve. This most commonly occurs within 7–10 days but has been noted as late as 2 weeks following surgery. If reliable conduction does not return, placement of a permanent pacemaker is generally necessary, even if there is a stable ventricular rhythm [65].
- **Atrioventricular Reciprocating Tachycardia** (**AVRT**) is a re-entrant tachycardia that involves both the AV node and an accessory pathway connecting the atria and ventricles. If the accessory pathway is capable of conducting in the antegrade direction during sinus rhythm (e.g. Wolf-Parkinson White Syndrome), the surface ECG may show ventricular pre-excitation. Tachycardia in most patients is initiated by a premature atrial beat that conducts antegrade over the AV node and then conducts retrograde via the accessory pathway back to the atria. Alternatively, AVRT may arise from a premature ventricular beat that conducts retrograde over the accessory pathway back to the atria and then antegrade via the AV node to the ventricle. Most commonly, AVRT is orthodromic, with antegrade conduction down the AV node and retrograde conduction up the accessory pathway back to the atria. Since antegrade conduction occurs down the AV node, QRS complexes are narrow and identical to those seen in sinus rhythm. In rare instances, the tachycardia is antidromic, with antegrade

conduction down the accessory pathway and retrograde conduction up the AV node back to the atria leading to a wide QRS complex. Patients with AVRT will manifest a short RP interval with a VA relationship of 1:1. Given the post-operative changes to the QRS complex morphology and duration, a comparison of the ECG in tachycardia to the initial post-operative study is often helpful. The treatment of patients with hemodynamically stable AVRT is adenosine (50–300 mcg/kg) or atrial overdrive pacing. Both these maneuvers break the re-entrant circuit by placing an area into relative refractoriness, thereby allowing sinus rhythm to reemerge. If these methods fail to break the tachycardia or are not available rapidly enough to treat an unstable patient, synchronized direct current cardioversion with 0.5–2 J/kg should be performed. Recurrent or refractory tachycardia may necessitate treatment with long-acting anti-arrhythmic medication.

- **Ventricular Tachycardia** (**VT**) is a wide complex tachycardia and is most commonly seen in conjunction with ventricular dysfunction and poor hemodynamics (e.g. cardiomyopathy, ventricular surgery, coronary anomalies with ischemia, tamponade) or in markedly hypertrophied ventricles. An unstable patient with a wide complex tachycardia should be presumed to have VT and treated immediately with direct current cardioversion at 2–4 J/kg. Amiodarone and lidocaine may be indicated as well. A thorough search for underlying treatable causes, particularly electrolyte abnormalities and myocardial ischemia is indicated.

Pacing

The use of temporary pacemakers is common in the treatment of post-operative cardiac patients, and the intensive care physician needs to be familiar with the use of these devices. The majority of patients who undergo cardiac surgery are returned to the ICU with temporary pacing wires in situ. The wires are placed in a standard manner with the atrial (**A**) wires to the patient's right and the ventricular (**V**) wires to the left, although this may be reversed in dextrocardia patients. If internal temporary pacing wires are not present, emergency electrical access can be obtained with either an esophageal lead for atrial pacing, or with transcutaneous pads for ventricular pacing.

Pacemakers fulfill two fundamental functions: discharging an electrical impulse for pacing a heart chamber and sensing the heart's electrical activity. In general, it can be thought of as a series of timers set to a certain cycle length (inversely related to heart rate). During the countdown of the timer, the pacemaker can be programmed to sense for an electrical event, and if none occurs before the timer reaches zero, a paced event occurs. Pacemakers, either temporary or permanent (implanted), can be programmed into numerous pacing modes based on a standard.

North American Society of Pacing and Electrophysiology/ British Pacing and Electrophysiology Group Generic Code: {P, S, R}, where P is the chamber paced – **A** (Atrium), **V** (Ventricle) or **D** (Dual); S is the chamber sensed – **A**, **V**, **D**, or **O** (none); and **R** is the response to sensing – **I** (Inhibit), **T**(Trigger) or **D**(Dual). As a general rule, bedside physicians should use the simplest pacing modes available to achieve adequate hemodynamics and avoid complications associated with more complex settings. Commonly used pacing modes and examples of situations in which they might be indicated are as follows:

- **AAI** – Senses the **A**trium, and paces the **A**trium if the sensed rate falls below the set default rate. *Indication*: *Sick sinus syndrome*, (*relative*) *sinus bradycardia*, *junctional ectopic tachycardia* (*JET*).
- **AOO** – Paces the **A**trium at the set default rate with no sensing. *Indication*: *Junctional ectopic tachycardia* (*JET*).
- **VVI** – Senses the **V**entricle, and paces the **V**entricle if the sensed rate falls below the set default rate. *Indication*: *Ventricular backup*, *usually for sinus rhythm with unreliable AV conduction* (*such as recovering heart block*).
- **DDD** – Senses the **A**trium and paces the **V**entricle. Will pace the **A**trium if the rate falls below the set default rate. More complex settings can be obtained, such as pacing the **V**entricle at a rate lower than the sensed **A**trial rate. *Indication*: *Heart block*.

During emergency pacing, maximum output is used to optimize capture of electrical activity and all sensing and responses are turned off. As with elective pacing, the stimulated chamber can include the atrium (AOO), ventricle (VOO) or both (DOO).

Repeated evaluation of the pacemaker's output and sensing thresholds is imperative as settings can change over time and following procedures (e.g. chest closure). Pacing thresholds may be checked by decreasing the output until there is loss of electrical capture. The threshold is considered the minimum output required to have consistent capture. Take note of the threshold output, and then set the output at two times the threshold or a minimum of 5 mA. Testing sensing thresholds may be more difficult, as it requires the patient to tolerate being in the underlying rhythm for a brief duration. With the pacemaker rate set below the intrinsic heart activity, the sensitivity is slowly decreased (higher value) until pacing is detected (secondary to loss of sensing). The threshold is the maximum sensitivity that maintains consistent sensing.

When programming a pacemaker for dual chamber pacing, it is also necessary to be aware of the upper rate limit, the AV interval and the post-ventricular atrial refractory period (PVARP). The upper rate limit is the fastest atrial rate,

or shortest cycle length that can be sensed by the pacemaker and needs to be set appropriately high for the patient and situation. Failure to do this may cause some atrial activity to be not sensed by the pacemaker leading to inappropriate pacing of either the atrium or the ventricle. The minimum cycle length that can be sensed or paced is the sum of two components, the AV interval and the PVARP, but can be manually set to an even longer interval than the sum of these two components. The first component of the cycle length, the AV interval, is the amount of time between an atrial event (paced or sensed) and a paced ventricular event. This is analogous to the PR interval on the ECG and should generally be set at a physiologic length. Longer AV intervals may be helpful in giving time for stiff, non-compliant ventricles to fill. The second component of the cycle length is the PVARP. The PVARP is the interval following a ventricular event (paced or sensed) during which sensing in the atrial lead is turned off. The PVARP ensures that the ventricular event will not be sensed by the atrial lead via retrograde conduction, which would set up a pacemaker-mediated tachycardia (PMT). PMT is essentially AVRT with the pacemaker serving as the accessory connection.

Duration of pacing is dependent on the patient's underlying rhythm, hemodynamic status, and goals of pacing. When pacing above an intrinsic rhythm, regular re-evaluation may be necessary to detect underlying changes. This can be achieved by slowly decreasing the pacing rate while observing for emergence of intrinsic activity and hemodynamic stability. A slow unstable rhythm may be suppressed by pacing, therefore sudden cessation to pacing output, either by disconnecting the pacing wires or use of the "pause" option on certain pacemakers, may be associated with a prolonged period of no cardiac activity. Higher thresholds may then be necessary to achieve capture (Wodinsky effect). Therefore, this should be avoided, as it can be misrepresent the true activity and lead to circulatory embarrassment.

Sedation, Analgesia and Muscle Relaxation

Post-operative patients require pain control and often require sedation. The principles of pain management for the post-operative cardiac patient are similar to those for other types of post-operative patients with the primary goal being patient comfort and safety. Occasionally, however, the physiologic or anatomic (delayed sternal closure) state of the patient requires that they remain more or less under general anesthesia. Neonates have been shown to exhibit detrimental hemodynamic effects from high circulating levels of stress hormones, and older patients with limited cardiac output and myocardial reserve may also benefit from treatment that limits their oxygen consumption. High dose narcotics and benzodiazepines can depress the release of intrinsic catecholamines, and hence decrease SVR and afterload, with an improvement in cardiac output. Further, increasing chest wall compliance with sedation and muscle relaxation may result in improved ventilation, particularly in the face of pulmonary hypertension or parenchymal lung disease. The presumed clinical course of the patient will determine whether a short or long-acting preparation (e.g. fentanyl vs. morphine) is used, and how the drug is administered (bolus vs. continuous infusion). Typically, morphine and midazolam are the analgesic/sedative combination used in the early post-operative period, with the ultimate dose titrated to effect. Fentanyl or morphine infusions are often used when there is the expectation of a prolonged need for anesthesia. Muscle relaxation is used to improve chest wall compliance as described above, but may mask the need for higher doses of narcotics or benzodiazepines.

As previously mentioned, early extubation has been shown to be safe and efficacious in the post-operative management of infants and children. As such, use of shorter acting agents, or drugs with less respiratory depression has become more desirable. Use of Dexmedetomidine, an intravenous α-2 adrenergic agonist has increased significantly for its ability to sedate without compromising respiratory drive. It has proved efficacious in limiting the amount of opioid and benzodiazepine administration, however facilitation to earlier extubation remains unclear [66–68].

Identification and Treatment of Low Cardiac Output Syndrome

Low cardiac output syndrome (LCOS) is defined as the inability of the myocardium to provide adequate oxygen delivery to the systemic tissues. LCOS in the early post-operative period is due primarily to transient myocardial dysfunction, compounded by acute changes in myocardial loading conditions, including post-operative increases in systemic and/or PVR. Residual cardiac abnormalities, even if minor, may further aggravate an underlying low output state. Surgical repair of cardiac malformations exposes the myocardium to periods of ischemia, resulting in transient myocardial stunning or damage. CPB activates the complement and inflammatory cascades [17, 19] thereby also contributing to myocardial injury, alterations in pulmonary and systemic vascular reactivity, and pulmonary dysfunction [20, 69–71]. In addition, some repairs require ventriculotomy, which further exacerbates myocardial systolic and diastolic dysfunction. Although advances in myocardial protection, cardioplegia, and perfusion techniques have dramatically reduced peri-operative cardiovascular injury, even relatively simple cardiac procedures are still associated with measurable myocardial dysfunction [72].

Prompt recognition and diagnosis of LCOS is a fundamental component of cardiac intensive care. Optimal post-operative management includes continuous monitoring of pulse oximetry, end-tidal CO_2, atrial and arterial waveforms, and multiple ECG leads [73]. Pulmonary arterial pressure monitoring is useful in selected patients [74]. At present, direct measures of myocardial performance and/or cardiac output in children is primarily a research tool and not feasible for routine clinical monitoring of patients. Therefore, cardiac output and systemic perfusion are usually assessed indirectly by monitoring vital signs, peripheral perfusion, urine output, and acid-base status. While post-operative LCOS may cause hypotension, systemic blood pressure is a particularly poor indicator of systemic perfusion in children who can markedly increase their systemic vascular tone. Hypotension and bradycardia tend therefore to be late consequences of LCOS, frequently occurring only minutes before cardiac arrest. Intractable cardiogenic shock results in unrelenting metabolic acidosis and ultimately multi-organ system failure, including acute renal failure, gastrointestinal complications and central nervous system compromise. Since LCOS is magnified in patients with palliated physiology or residual cardiac abnormalities, multi-organ system failure is more likely in such patients.

Low cardiac output after congenital heart surgery is usually due to related and interacting factors. Although defects in myocardial systolic contractile or diastolic function usually accompany LCOS, myocardial contractile dysfunction should always be considered a diagnosis of exclusion and other potential causes of LCOS, such as altered ventricular loading and residual cardiac lesions, should be ruled out when initiating therapy with inotropic, lusitropic, or vasoactive agents. Changes in ventricular loading are integral to myocardial performance after congenital heart surgery. Ventricular preload is often inadequate, due to blood loss, peri-operative fluid shifts, changes in diastolic compliance or physiologic changes resulting from the surgical procedure (e.g. Fontan or shunted single ventricle physiology) [75]. Cardiac tamponade, which impairs preload by altering diastolic compliance, should also be considered in patients showing signs of LCOS. Increases in intrathoracic pressure resulting from blood/fluid tamponade or pneumothorax will limit venous return and impede ventricular filling. Myocardial tamponade can result from diffuse intrathoracic fluid accumulation or a localized collection of blood clot or fluid that limits venous return to one or more chambers of the heart in a selective manner.

Ventricular afterload is often increased after CPB procedures, resulting from CPB-mediated vascular injury and the resultant altered vascular reactivity. Both systemic and pulmonary endothelial dysfunction have been observed following CPB with or without circulatory arrest, presumably resulting from ischemia-reperfusion injury to the endothelium [21, 76–79]. Systemic vasoconstriction raises the afterload on the left or systemic ventricle, while pulmonary vasoconstriction increases afterload on the pulmonary or RV. A pulmonary hypertensive crisis causes an acute rise in RV afterload, which shifts the interventricular septum from right-to-left into the systemic ventricle, substantially decreasing the preload of the systemic ventricle. The acute increase in RV afterload and decrease in left ventricular preload can diminish cardiac output dramatically. A pulmonary hypertensive crisis most often presents with acute systemic hypotension and diminished perfusion. Arterial oxygen saturation will decrease only when right-to-left intracardiac shunting can occur.

Residual anatomic or electrophysiologic abnormalities are likely to diminish cardiac output after congenital heart surgery. Uncorrected anatomic defects such as outflow obstruction or valvar insufficiency reduce the effective stroke volume and/or increase the cardiac workload required to provide adequate systemic blood flow. Similarly, persistence of a left-to-right intracardiac shunt or an elevated Qp:Qs ratio will yield excessive pulmonary blood flow and thus diminish systemic blood flow. Low cardiac output could be exacerbated by arrhythmias, which limit ventricular filling and/or compromise atrioventricular synchrony. Arrhythmias are relatively common after congenital heart surgery [62, 80, 81]. Certain rhythm disturbances, particularly JET and complete heart block are associated with LCOS. Careful evaluation for residual cardiac abnormalities is indicated in any patient with low cardiac output, especially when patients do not follow their expected post-operative course after heart surgery.

The initial step in management of LCOS is to determine the adequacy of the intravascular volume. Inadequate preload is common in post-operative cardiac surgical patients. Potential causes of post-operative hypovolemia include bleeding, excessive ultrafiltration, and vasodilation from rewarming or afterload reduction [75]. Failure to provide adequate preload cannot be compensated for by utilizing inotropic and vasoactive drugs. Indications that preload is inadequate include tachycardia, dry lips and mucous membranes, sunken fontanel and/or eyes, low blood pressure and filling pressures, and ongoing blood loss. Filling pressures must be interpreted with some caution, in that hypertrophied ventricles, or ventricles with high pre-operative filling pressures almost always require higher than normal post-operative filling pressures. Ongoing third space losses of fluid represent a challenge, since these are not readily accounted for by measurement of fluid intake and output, and can result in a patient who has excess body edema but intravascular volume depletion. Repletion of intravascular volume with colloid is the most common approach to volume resuscitation in the post-operative pediatric cardiac patient, but crystalloid solutions are used in some institutions. Blood

loss should be replaced with packed red blood cells and other blood-products as necessary.

Myocardial contractility can be enhanced by using β-adrenergic agonists or phosphodiesterase inhibitors. Low-dose dopamine (≤5 mcg/kg/min), dobutamine and epinephrine (≤0.05 mcg/kg/min) all increase contractility via stimulation of myocardial β-adrenergic receptors but do not significantly stimulate vascular α-adrenergic receptors, thereby minimizing associated vasoconstriction. Epinephrine may be preferred over dopamine as it may improve cardiac output without increasing systemic oxygen consumption [82]. Cardiomyocyte contractility and relaxation occur because of rapid calcium cycling within the cells. During electrical systole calcium is rapidly made available to the contractile apparatus and facilitates the interaction of actin and myosin. During diastole, calcium is actively removed from the cytoplasm, thus facilitating cellular relaxation. β-adrenergic agonists work by increasing intracellular cyclic adenosine monophosphate (cAMP), which subsequently increases calcium cycling in both systole and diastole. Since cAMP is degraded by phosphodiesterases, phosphodiesterase inhibitors such as milrinone (0.25–0.75 mcg/kg/min) also increase cAMP and have many of the same effects as β-adrenergic agonists [83]. One particular advantage of phosphodiesterase inhibition is that it is not receptor dependent and therefore not altered by the type of receptor down regulation that occurs during chronic adrenergic stimulation. Milrinone has been shown to prevent LCOS following repair of CHD [84]. β-adrenergic receptors also mediate systemic vasodilatation so that another advantage of these drugs is that they promote afterload reduction for the systemic (and perhaps pulmonary) ventricle [85].

Since the goal of management of LCOS is to maximize systemic perfusion, it is often the case that optimal management is associated with low normal blood pressure. Blood pressure is the product of cardiac output and SVR. In addition, there is an inverse relationship between SVR and stroke volume. Therefore, use of vasodilators for afterload reduction results in an increase in stroke volume, cardiac output and systemic oxygen delivery, albeit often at a lower blood pressure. When vascular tone is high, either intrinsically or secondary to the use of higher doses of adrenergic agonists, and cardiac output is low, pure vasodilating agents can be used to improve oxygen delivery. Nitroprusside, nitroglycerine and phenoxybenzamine or phentolamine are commonly used at many centers for this purpose, particularly in combination with epinephrine or norepinephrine to boost contractility [45, 46].

When blood pressure is too low to maintain adequate organ perfusion it is preferable to maximize preload and contractility before resorting to increasing SVR. Again, this is because of the inverse relationship between afterload and cardiac function and the likelihood that the increase in blood pressure will come at the cost of a further decrease in cardiac output and oxygen delivery. An exception to this relationship occurs when coronary perfusion has become critically low and an increase in blood pressure can improve myocardial function. In this situation, it is sometimes necessary to increase SVR to achieve an acceptable blood pressure. This is most common when there are concurrent issues such as sepsis, but vasodilatory shock has also been reported after CPB. Commonly used vasopressors include epinephrine and norepinephrine (which also have significant β-agonist effects), phenylephrine and arginine vasopressin [86, 87]. Persistent hypotension refractory to catecholamines should lead one to consider abnormalities in adrenal or thyroid function [88]. Supplementation with hydrocortisone in particular has shown some promise in treating refractory hypotension not due to other identifiable causes [89].

Calcium supplementation may also be beneficial in patients with post-operative myocardial dysfunction, particularly neonates. The neonatal heart has an immature calcium handling system and is more dependent on extracellular calcium for contractility than is the mature heart [90]. Hypocalcemia occurs frequently in the post-operative period and may be pronounced in patients with 22q11 deletion syndrome and in neonates with transient hypoparathyroidism. Transfusion of citrate-treated blood, which chelates calcium, and administration of loop diuretics may exacerbate the hypocalcemia. Ionized calcium, the physiologically active form of calcium, should be monitored frequently in the post-operative period and normal or supranormal levels maintained with supplementation when this is a concern. Many centers routinely use calcium infusions in neonates after cardiopulmonary bypass to augment and stabilize extra-cellular ionized calcium, especially in patients with 22q11 deletion syndrome.

Acute Kidney Injury

The post-operative course of children undergoing bypass surgery may be complicated by acute kidney injury (AKI), which has been associated with increased morbidity and mortality [91, 92]. The pathophysiology of CPB-induced AKI is multifactorial and involves ischemia-reperfusion injury, oxidative stress, and activation of the systemic inflammatory response. The kidney is particularly sensitive to these effects, and non-pulsatile flow during CPB contributes further to tubular epithelial injury through renal artery vasoconstriction, worsening the ischemia/reperfusion injury. Infants and children undergoing CPB for repair or palliation of cyanotic CHD are especially vulnerable to developing AKI since they can require multiple surgeries for step-wise repair of complex congenital anomalies. Patients may also be predisposed to renal injury because of underlying congenital

nephropathy or concurrent use of nephrotoxic agents (e.g. aminoglycosides, vancomycin, and furosemide). Clinically, AKI manifests with low urine output and increasing serum creatinine levels. This may limit effective diuresis and volume management, cause electrolyte imbalances, and may necessitate renal replacement therapy. Recently, the use of several plasma and urine biomarkers reflecting renal injury has increased, allowing earlier identification of insult and affording an opportunity to modify its natural history [93]. The most promising of these to date, Neutrophil Gelatinase-Associated Lipocalin (NGAL), has been shown to rise within 2 h of the onset of CPB in in children with AKI following cardiac surgery and the magnitude of increase has correlated with disease severity and morbidity [93, 94].

Diuretics

Diuretic therapy is usually started on the first post-operative day when changes in cardiovascular status and fluid shifts have stabilized. Diuretics are often necessary to help decrease accumulated lung water that occurs as a consequence of CPB, to treat ongoing pulmonary edema secondary to alterations in ventricular function or because of sensitization of the kidneys due to pre-operative diuretic use. Loop diuretics such as furosemide (1–2 m/kg/dose q6–q12) are the most commonly used, but are often supplemented with thiazide diuretics such as chlorothiazide (2–5 mg/kg/dose, q6–q12) for synergistic effects. Loop diuretics may be administered as a continuous infusion in patients who become hypotensive as a result of fluid shifts associated with bolus doses. Failure to respond to diuretics should lead to re-assessment of the patient's volume status and cardiac output, since hypovolemia and low cardiac output are the main causes of oliguria despite diuretics. Diuretic treatment is associated with predictable metabolic derangements (e.g. hypokalemia, hyponatremia, hypocalcemia, hypomagnesaemia, and metabolic alkalosis), which should be accounted for and treated.

Line and Tube Removal

In-dwelling lines, catheters and wires are removed when they are no longer required. The patient should be observed closely after transthoracic atrial lines are removed, due to the risk of bleeding and pericardial tamponade. Pulmonary artery lines have the highest incidence of complications, followed by left atrial lines and finally right atrial lines [74]. Removal of mediastinal and pleural chest tubes should be done with recognition of the risk of pneumothorax. A chest radiograph is sometimes performed after removal of these tubes to check for the presence of any intra-thoracic air collections. Persistent chest tube drainage suggests elevated right-sided filling and central venous pressures or significant venous occlusion.

Mechanical Circulatory Support

Extracorporeal membrane oxygenation (ECMO) is a form of CPB that is used regularly in intensive care settings to support patients with cardiopulmonary failure who have inadequate gas exchange and/or low cardiac output. Support can be instituted in a compromised or deteriorating patient before cardiac arrest, or during active cardiopulmonary resuscitation, referred to as ECPR. The system utilizes a rotary or centrifugal pump to drive blood through a low resistance oxygenator prior to returning to the patient. Individuals with impaired oxygenation or ventilation in the setting of adequate heart function drain systemic venous blood prior to returning oxygenated blood back to right sided circulation, which is known as veno-venous ECMO (VV-ECMO). Those with poor cardiac performance will drain systemic venous veins and supply arterial perfusion, which is known as veno-arterial ECMO (VA ECMO). ECMO provides a short-term bridge to recovery, transition to a ventricular assist device, or transplantation. The progressively increasing risks of bleeding in setting of systemic anticoagulation, thromboembolic disease (i.e. stroke), and secondary organ failure generally limit its use to under 2 weeks but individual patients can be supported for many weeks if no limiting complications arise. Survival from ECMO for pediatric cardiac surgery patients is approximately 40–50 % [95–97].

Children who require longer support are often transitioned to ventricular assist devices (VADs). These devices can be configured as a single or biventricular support. The largest body of experience with pediatric VADs is with the Excor© pneumatic pump by Berlin Heart [98]. The Thoratec Heartmate©, Heartware©, Abiomed Impella© and aortic balloon pumps have successfully supported older pediatric patients. These devices use pneumatic or centrifugal technology to augment ventricular outflow.

Recently, the iLA ventilator by Novalung© has successfully supported pediatric patients with oxygenation or ventilatory failure. In its usual configuration, arterial blood flows down its pressure gradient, through the low resistance membrane, into a central venous catheter (femoral-femoral). However, in isolated cases, pulmonary artery to left atrium cannulation has been employed to support patients with pulmonary hypertension as a bridge to lung transplantation [99].

Lesion-Specific Post-operative Care

One of the most important aspects of intensive care management following surgery for CHD is the recognition that specific lesions and operations are associated with specific

post-operative anatomic and physiologic complications. Despite the lengthy list of potential anatomic types of CHD and surgical repairs, the types of post-operative complications generally fall into certain categories. The following section will briefly review some of the more common anatomic and physiologic issues that need to be anticipated following certain operations.

Residual Left-to-Right Shunt

Residual left-to right shunts can occur after operations that involve repair of septal defects, when pre-operative shunts are left unrepaired or when there are unrecognized or untreated systemic to pulmonary artery shunts (such as aortopulmonary collaterals). The mechanisms by which such shunts can be problematic include the development of pulmonary edema secondary to increased pulmonary blood flow, pulmonary hypertension, volume overload of the systemic ventricle and, in certain circumstances, limitation of systemic cardiac output. Common signs or symptoms include a pulmonary outflow or ventricular septal defect murmur, high systemic atrial pressure, hepatomegaly, and cardiomegaly with increased pulmonary vascularity on chest radiograph.

Atrial level shunts are rarely a problem unless they are associated with factors that cause left atrial hypertension thereby driving the shunt and maintaining high pulmonary artery pressures. Congestive heart failure and pulmonary overcirculation secondary to an atrial left-to-right shunt should therefore lead one to carefully evaluate the patient for mitral stenosis or insufficiency, inadequate systemic ventricular size, poor systemic ventricular function or systemic ventricular outflow tract obstruction with elevated end-diastolic pressure.

Making the diagnosis of a residual shunt should lead to discussion regarding the risk-benefit balance of attempting further repair, either surgically or in the catheterization lab. Some lesions are not repairable, and the patient needs to be managed in such a way as to minimize the adverse consequences of the shunt. This may include avoiding therapy that lowers pulmonary resistance or that increases systemic resistance, either of which may aggravate the shunt. Prolonged inotropic support, mechanical ventilation and relatively large doses of diuretics are often necessary. As the heart recovers from the acute detrimental effects of surgery, the residual shunt may become better tolerated, allowing weaning of support.

Residual Systemic Ventricular Outflow Tract Obstruction

Residual systemic ventricular outflow tract obstruction should be looked for after all surgery to relieve outflow obstruction such as repair of subaortic stenosis, aortic stenosis or coarctation. Additionally, systemic ventricular outflow obstruction can occur after repair of atrio-ventricular septal defects or after other operations that remove large volume loads from the systemic ventricle when the underlying anatomy includes subvalvar hypertrophy. Signs and symptoms of systemic outflow obstruction include an ejection murmur and elevated systemic atrial pressure.

Mild systemic outflow obstruction is usually well tolerated, but more severe lesions can significantly impair cardiac output. Diagnostic studies including Doppler ultrasound and cardiac catheterization should focus on the anatomic features of the outflow tract, since low flow across even a severe obstruction may not produce a large gradient in the face of low cardiac output. Unlike adults with systemic ventricular outflow obstruction, use of β-adrenergic agonists is not usually associated with myocardial ischemia since cardiac output and myocardial oxygen delivery usually improve. Particular caution is necessary, however, when the obstruction is dynamic. Increased contractility can worsen this type of lesion and inotropic drugs may be contraindicated. Unfortunately, the presence of systemic ventricular outflow obstruction often limits the ability to use vasodilating agents for afterload reduction and may require vasopressor support. In this setting the systemic ventricular afterload is "fixed" at the level of the obstruction. Because of the inability of the ventricular output to increase, administration of vasodilators will often result in hypotension.

Tricuspid or Mitral Valve Dysfunction

Residual atrioventricular valve dysfunction, either insufficiency or stenosis, can occur after any attempted valve repair or when closure of a septal defect unmasks valvar stenosis on one side of the heart. Atrioventricular valve insufficiency is associated with high atrial pressures on the affected side of the heart. If atrial pressure is being directly monitored there will often be very prominent v waves on the tracing, and a regurgitant murmur will be heard. Because of the associated ventricular volume overload, there may be signs or symptoms of ventricular failure. Atrioventricular valve stenosis is also associated with high atrial pressure, but with prominent a waves. Peripheral (right-sided) or pulmonary (left-sided) edema is common with stenotic lesions and pulmonary hypertension occurs with mitral stenosis. When severe, either stenosis or insufficiency can limit cardiac output.

Medical management of atrioventricular valve insufficiency is focused on afterload reduction, with inotropic support when needed. Systemic vasodilators promote antegrade cardiac output in the face of mitral (or even aortic) insufficiency, whereas diuretics may be useful in either stenotic or regurgitant lesions. Atrioventricular valve stenosis is, in general, not particularly amenable to medical management,

although its consequences such as pulmonary hypertension may require aggressive treatment.

Right or Left Ventricular Diastolic Dysfunction

Ventricular diastolic dysfunction should be an expected complication of any operation where there is significant ventricular hypertrophy. This most commonly occurs after relief of obstructive lesions or when there is pre-existing diastolic dysfunction. Operations that require a right ventriculotomy in an already hypertrophied right ventricle (such as tetralogy of Fallot) are at particularly high risk for post-operative diastolic dysfunction.

Diastolic dysfunction is marked by elevated atrial pressure and has many of the same features seen in atrioventricular valve disease. The presence of a residual atrial shunt in this setting compounds the adverse effects of left-sided disease by promoting pulmonary over-circulation. An atrial defect can help maintain cardiac output when the RV is non-compliant at the expense of associated cyanosis. The need to maintain high pressure to promote adequate ventricular filling results in hydrostatic pressure favoring extravasation of fluid and leading to pulmonary edema in the case of left-sided problems and third-space losses of fluid when there is right ventricular diastolic dysfunction.

In general, the first line treatment for diastolic dysfunction is to maintain adequate preload, reduce afterload, and avoid tachycardia to allow for longer filling times. Systolic ventricular function is usually preserved if not hyperdynamic; therefore, use of inotropic agents should be minimized. Inotropic agents that reduce afterload (such as phosphodiesterase inhibitors) may be preferred for potential lusitropic effects that may improve diastolic function. Fluid administration can be limited by impairment of oxygenation and lung function with progressive pulmonary edema, or by complications of peripheral edema and third-spacing of fluid. Right-sided lesions in particular often respond very well to initial fluid boluses, but the hydrostatic forces in combination with diminished lymphatic drainage due to high venous pressure leads to pleural effusions and ascites. As these problems worsen, there is a need for progressively higher airway pressure to compensate for increased abdominal pressure and/or loss of effective lung volume. The high airway pressure is transmitted to the pulmonary vasculature because the pulmonary parenchyma is relatively healthy, and this in turn increases afterload on the already poorly functioning RV. Increased abdominal pressure and low cardiac output also result in decreased renal perfusion and eventually renal failure, further complicating fluid management. A downward spiral develops in which cardiac output cannot be readily restored and pulmonary gas exchange cannot be adequately maintained. Early separation from positive pressure ventilation can significantly reduce right ventricular afterload and increase systemic cardiac output [59]. Additional treatment can include drainage of effusions or ascites followed by further fluid resuscitation. In extreme cases mechanical support with a right-ventricular assist device or ECMO is necessary. In general, right-ventricular diastolic function often improves over several days as the ventricle heals from surgery and becomes more compliant. Left ventricular diastolic dysfunction may similarly resolve, but is more likely to be associated with prolonged heart failure and/or the need for transplantation.

Pulmonary Hypertension

The incidence of post-operative pulmonary hypertension has decreased as the fields of pediatric cardiology and cardiac surgery have moved toward earlier repairs of the left-to-right shunt lesions most often associated with chronic pulmonary vascular changes. Nevertheless, CPB can provoke pulmonary hypertension in those patients with significant underlying risk [79]. Neonates, patients with pulmonary venous obstruction or mitral valve disease, and those with elevated pre-operative pulmonary resistance are at particularly high risk, especially when associated with pain, agitation, suctioning, or hypoventilation. Signs and symptoms of pulmonary hypertension depend on the acuity of the change in resistance and on the underlying anatomy, particularly with regard to the existence of residual shunts. Chronic pulmonary hypertension that is not acutely worsened as a result of CPB can be well tolerated in the post-operative period, whereas acute pulmonary hypertensive crises can precipitate life-threatening symptoms. The presence of a patent foramen ovale, ASD, VSD or systemic to pulmonary artery shunt causes the main clinical consequence of acute elevations in PVR to be cyanosis because of an increase in right-to-left shunting. Pulmonary hypertension without shunting can cause acute right ventricular failure and low cardiac output without significant changes in saturation. A sudden fall in either blood pressure or saturation in a patient with known pulmonary vascular disease or with significant risk of post-operative pulmonary hypertension should prompt immediate consideration of this diagnosis and institution of treatment when appropriate. The presence of a pulmonary artery pressure-monitoring catheter can help establish the diagnosis of pulmonary hypertension. Most commonly, the systemic pressure falls while the pulmonary artery pressure remains unchanged. The increased ratio of pulmonary to systemic arterial pressure is diagnostic of an increase in PVR.

In addition to hypotension or cyanosis, a pulmonary hypertensive crisis in the absence of a right-to-left shunt is usually associated with an acute increase in right atrial pressure because the increase in right ventricular afterload raises

diastolic pressure. This can also result in shift of the ventricular septum into the left ventricle and a subsequent increase in left atrial pressure despite the decreased filling of the left side of the heart. Other clinical manifestations can include a sudden decrease in lung compliance and/or onset of bronchospasm. Since pulmonary hypertension is exacerbated by hypoxia and hypercarbia, these manifestations can be especially troublesome.

The most effective treatment strategy for those at significant risk of post-operative pulmonary hypertension is prevention. Maintenance of adequate analgesia and sedation, particularly during noxious stimuli such as suctioning is important. Induction of a respiratory alkalosis can be helpful in an acute pulmonary hypertensive crisis, but maintaining a pH above 7.5 for prolonged periods may have adverse consequences for cerebral perfusion. Therefore, a more practical approach is to avoid common problems that lead to hypoxia and respiratory acidosis such as pneumothorax, right mainstem bronchus intubation, or mucous plugging and to maintain a pH between 7.4 and 7.5. It is generally appropriate to try to normalize the pH and reduce sedation on a daily basis while carefully observing the patient for symptoms associated with increased pulmonary artery pressure. Continued problems with pulmonary hypertension for more than 4–7 days suggest important residual lesions or more chronic pulmonary vascular disease.

When prophylactic therapy fails, more aggressive treatment with inhaled nitric oxide, sildenafil, Bosentan or even mechanical support may be helpful. Most studies have shown low doses of nitric oxide (2–20 ppm) are as effective as higher doses (40–80 ppm) but are less likely to be associated with complications such as methemoglobinemia. Sildenafil and Bosentan can be used to transition from inhaled nitric oxide to chronic oral therapy for patients with chronic pulmonary vascular disease, since exogenous nitric oxide can lead to inhibition of endogenous production [100, 101]. Numerous other intravenous vasodilators including calcium channel blockers, nitro-vasodilators and prostaglandins have been used but are often limited by the occurrence of systemic hypotension because of lack of pulmonary selectivity. Prostacyclin has shown promise as an agent that may reverse pulmonary vascular changes previously thought to be permanent. Use of pulmonary vasodilators may be contraindicated when there is significant residual pulmonary venous obstruction or left atrial hypertension as acutely lowering arteriolar resistance can precipitate acute pulmonary edema.

Single Ventricle Lesions

Children with single-ventricle anatomy generally undergo a palliative surgery in the neonatal period to achieve the following: (1) unobstructed systemic blood flow; (2) regulated pulmonary blood flow to minimize the risk of pulmonary artery hypertension and ventricular volume overload; (3) non-distorted branch pulmonary arteries; (4) unobstructed pulmonary venous return; (5) unobstructed interatrial communication; and (6) a minimum of atrioventricular valve regurgitation. Essentially, the goal is to balance the pulmonary and systemic circulations (Qp:Qs). If there is insufficient pulmonary blood flow, the infant will be hypoxemic. If there is excessive pulmonary blood flow, it results in congestive heart failure. In infants with impaired systemic blood flow this is typically accomplished through a stage I Norwood type procedure with a modified systemic to pulmonary artery (Blalock-Taussig or BT) shunt or right ventricle to pulmonary artery shunt (RV-PA – Sano modification). A recent multi-center randomized controlled study demonstrated that early transplant free survival favored the RV-PA modification at the expense of increased early intervention; the difference to longer-term transplant-free survival was unclear [102]. An emerging hybrid procedure combines catheter-based stenting of patent ductus arteriosus with surgical peripheral pulmonary artery banding [103, 104]. Infants with pulmonary over-circulation can undergo pulmonary artery banding as staged palliation. Since each anatomic arrangement establishes similar physiology, the important differences between them are in the means by which each operation accomplishes its goals. The Norwood operation requires CPB, cardioplegia and a period of DHCA, although regional cerebral perfusion techniques can limit circulatory arrest time [105–107]. The heart, kidneys, brain and other organs including the systemic and pulmonary endothelium undergo a period of ischemia followed by reperfusion often followed by a defined period of myocardial, renal and perhaps endothelial dysfunction in the post-operative period. A BT shunt, either alone or as part of a Stage I Norwood procedure, often results in low diastolic arterial pressure, which may compromise coronary perfusion. Unlike a BT shunt, a right ventricle to pulmonary artery conduit relies exclusively on systolic pulmonary blood flow and maintains increased systemic diastolic pressures; nevertheless, pulmonary arterial growth and volume loading of ventricle may be undesirable complications. The hybrid pathway delays the use of cardiopulmonary bypass beyond the neonatal period to a larger second stage palliation in hopes of improving cerebral protection [108]. Banding of pulmonary artery in univentricular hearts may increase the risk of subaortic obstruction and ventricular hypertrophy [109], although this has also been disputed [110]. Both shunts and bands carry the risk of unilateral pulmonary artery obstruction and this should be included in the differential of late cyanosis after either of these procedures.

Single ventricle lesions encompass distinctly different physiologies depending on the stage of palliation. After procedures involving a Norwood operation, hybrid palliation, BT shunt or pulmonary artery band, the pulmonary to

systemic blood flow ratio (Qp:Qs) is dependent on the SVR, the size of the systemic to the pulmonary artery connection and to a lesser degree, the PVR. The arterial saturation is essentially an average of the pulmonary and systemic venous saturations weighted by the Qp:Qs, so that anything that decreases mixed venous saturation, pulmonary venous saturation or Qp:Qs can result in increased cyanosis. Problems in the post-operative period that can lead to impaired oxygen delivery include low systemic cardiac output and/or excessive cyanosis. It is important to determine if the problem is primarily related to a low total cardiac output, inappropriate systemic to pulmonary blood flow ratio (low or high Qp:Qs) or to pulmonary venous desaturation. Impaired systemic perfusion or a widened arterial-mixed venous oxygen saturation difference suggest impaired systemic blood flow, which may occur as a result of low total cardiac output or an inappropriately high Qp:Qs. Since the mixed venous oxygen saturation is low in both circumstances, the patient will often be cyanotic in addition to poorly perfused. On the other hand, cyanosis with preserved hemodynamics and perfusion suggests low pulmonary blood flow (decreased Qp:Qs) and/or to pulmonary venous desaturation.

Although management of newborn single ventricle physiology once focused on manipulation of Qp:Qs via manipulation of PVR, current management is directed toward improving total cardiac output (Total Q = Qp + Qs) and lowering SVR [45]. Afterload reduction can increase stroke volume thus improving total cardiac output while simultaneously decreasing Qp:Qs, by decreasing SVR and increasing Qs while not significantly lowering Qp. Therapeutic strategies aimed at maximizing PVR are of limited value in practice, particularly since the largest component of the pulmonary resistance occurs at the site of the band or shunt.

Second and third stage palliation for single ventricle lesions result in pulmonary blood flow that is dependent on non-pulsatile venous return. A unique aspect of the physiology of the bidirectional cavopulmonary anastomosis (Glenn shunt) is that pulmonary blood flow is largely dependent on the resistance of two highly but differentially regulated vascular beds. Both the cerebral and pulmonary vasculature has opposite responses to changes in carbon dioxide, acid-base status and oxygen. This can make treatment of elevated pulmonary resistance or low arterial saturation particularly challenging. Hyperventilation and alkalosis for example, may have limited utility in this setting. Although they are effective pulmonary vasodilators, hyperventilation and alkalosis cause cerebral vasoconstriction [111]. Since Qp is dependent on venous return via the superior vena cava (largely made up of cerebral blood flow), maneuvers that limit cerebral blood flow may decrease pulmonary flow and exacerbate hypoxemia [112]. Other frequently used techniques for decreasing PVR such as deep sedation/anesthesia may also reduce cerebral blood flow and therefore fail to increase Qp even if they successfully reduce resistance. Inhaled nitric oxide, which acts selectively on the pulmonary vasculature, has been reported to be effective in reducing the transpulmonary pressure gradient for patients after the bidirectional cavopulmonary anastomosis and may therefore be the best treatment for high pulmonary resistance and hypoxemia [113]. In the patient with normal PVR, mild hypoventilation will generally result in improved cerebral blood flow and increased pulmonary blood flow [58]. Patients with a cavopulmonary anastomosis will also benefit from return to spontaneous ventilation as soon as their clinical state allows [114].

When a significant left-to-right shunt persists following bidirectional cavopulmonary anastomosis because of additional sources of Qp or aortopulmonary collateral blood vessels, persistent pleural effusions, high central venous pressures and low cardiac output may result [115–117]. It is also important to recognize that there are changes in ventricular geometry that occur with these operations because of reduction in left-to-right shunt, particularly with the bidirectional Glenn. When systemic outflow is dependent on flow through a ventricular septal defect or bulboventricular foramen, acute decreases in ventricular dimension may precipitate effective sub-aortic stenosis. The appearance of an ejection murmur in a patient with susceptible anatomy following bidirectional cavopulmonary anastomosis should prompt a complete assessment for this phenomenon.

Fontan physiology is a hybrid of bidirectional Glenn and normal cardiovascular physiology. Like the bidirectional Glenn, Qp is dependent on systemic venous pressure, and all Qp is effective [118]. If the Fontan baffle is fenestrated, there may still be a right-to-left shunt causing some mild systemic arterial desaturation, but the systemic and pulmonary circulation are largely separated, as with a normal heart. Important issues for the intensive care physician arise when there is elevated pulmonary artery pressure. This can occur in the setting of elevated PVR, anatomical pulmonary artery obstruction or with elevated pressures in the pulmonary venous atrium due to myocardial dysfunction. Numerous studies have demonstrated an association between elevated pulmonary artery pressure (>10–15 mmHg) and poor outcome in Fontan patients [119–121], largely due to third space losses of fluid that occur with elevated central venous pressures. As these fluid losses progress, patients develop pleural effusions, ascites and generalized edema. In the face of a full abdomen, heavy chest wall and smaller effective pleural cavities, it often becomes necessary to increase ventilator pressures to maintain adequate functional residual capacity and tidal volume. Increased intrathoracic pressure, particularly in the absence of parenchymal lung disease than effectively raises pulmonary resistance and necessitates even higher venous pressures to maintain cardiac output, creating a vicious circle. Furthermore, as central venous and

intra-abdominal pressure rise, renal perfusion pressure decreases, especially in the face of low cardiac output and borderline hypotension. In general, Fontan fenestration can lower the risk of some of these complications by providing a source of Qs that is not dependent on passing through the pulmonary circulation [122, 123]. Fenestration can also decrease pulmonary artery pressure enough to reduce third space losses of fluid.

When an individual with Fontan physiology is in a low cardiac output state, it is essential to determine and treat the underlying cause. It is common for post-operative Fontan patients to need large amounts of volume in the first day after surgery, particularly when they remain on positive pressure ventilation. Persistently low central venous and left atrial pressures strongly suggest the need for volume. Pulmonary artery obstruction should be considered as the cause of low output when left atrial pressure is low and central venous pressure is high. If central venous pressure is not monitored, large third-space fluid losses with a low or normal left atrial pressure should raise the suspicion of this diagnosis. Even in the presence of a fenestrated Fontan, the capability of the fenestration to preserve cardiac output in the face of anatomic or physiologic obstruction to pulmonary blood flow is significantly limited compared to the situation after the bidirectional cavopulmonary anastomosis. Therefore, limited pulmonary flow can result in low cardiac output and, when a fenestration is present, significant cyanosis. Cyanosis can also result from intrapulmonary arteriovenous malformations or ventilation-perfusion mismatch related to low cardiac output [124, 125].

If high pulmonary resistance is responsible for the elevation of central venous pressure, institution of the standard therapies of supplemental oxygen, hyperventilation and alkalosis is indicated. As with the bidirectional Glenn patient, the use of high positive pressures to achieve these ends may be counter-productive. Negative pressure ventilation can augment stroke volume and cardiac output and high-frequency jet ventilation may lower $PaCO_2$ at low mean airway pressures [60, 126, 127]. Intravenous vasodilators such as prostacyclin or PGE should be used with caution because of the risk of systemic vasodilation with limited cardiac output. Inhaled nitric oxide has been reported to be effective in lowering the transpulmonary pressure gradient [128].

Low cardiac output with high left atrial and central venous pressures indicates myocardial dysfunction in the patient with Fontan physiology. Myocardial dysfunction can occur from ischemia-reperfusion injury if aortic cross clamping and cardioplegia are used to create the Fontan baffle. It may also be related to poor pre-operative myocardial function. The only effective long-term therapy for low cardiac output with ventricular dysfunction following a Fontan operation is to improve cardiac output and reduce left atrial pressure. The use of inotropic agents that do not increase ventricular afterload, such as phosphodiesterase inhibitors, dobutamine and low dose epinephrine ($\leq$0.05 mcg/kg/min) may be helpful. If systemic blood pressure will tolerate it, aggressive afterload reduction with vasodilating agents may also lower left atrial pressure significantly. If there is good reason to believe the insult to ventricular function is reversible, mechanical circulatory support can also be effective therapy. Because persistent aortopulmonary collateral vessels can be associated with hemodynamics similar to those of ventricular dysfunction, aggressive assessment and embolization of these vessels may be useful in this situation [129–131].

Conclusion

The management of the post-operative pediatric cardiac surgical patient requires a comprehensive understanding of the basic principles of oxygen delivery, cardiovascular physiology and the anatomy and physiology of CHD. Signs and symptoms of LCOS should be treated aggressively and diagnostic and therapeutic strategies should address both universal and lesion-specific problems.

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Part V

Critical Care of the Solid Organ Transplant Patient

Denis Devictor

Pharmacology of Immunosuppression

26

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Abstract

As discussed in the subsequent chapters of this section, transplant of solid organs has emerged to become a viable and very realistic option for the treatment of a variety of disorders. The outcomes from transplantation of solid organs, including Heart, Heart/Lung, Lung, Kidney, Liver, Small Bowel, Liver/Small Bowel/Pancreas have improved significantly with time. To a large measure, the successes in solid transplant programs have occurred concomitantly with advances in surgical techniques and prevention of acute and chronic allograft rejection. As many of these children are cared for in the Pediatric Intensive Care Unit (PICU) environment, both immediately after as well as with the myriad of potential complications and long-term problems that may occur, clinicians working in the PICU must have an in-depth understanding of the pharmacology of immunosuppressive medications as well as their potential adverse effects.

Keywords

Immunosuppression • Cyclosporine • Tacrolimus • Sirolimus • Mycophenolate mofetil • Azathioprine • Monoclonal antibodies

Introduction

As discussed in the previous chapters of this section, transplant of solid organs has emerged to become a viable and very realistic option for the treatment of a variety of disorders. The outcomes from transplantation of solid organs, including Heart, Heart/Lung, Lung, Kidney, Liver, Small Bowel, Liver/Small Bowel/Pancreas have improved significantly with time. There was a dramatic increase in the success of solid organ transplantation beginning in 1980. While advancements in surgical techniques and organ preservation almost certainly played a role in this increased success, it is clear that the greatest factor responsible for the improvement in outcomes following solid organ transplantation was the introduction of a more potent and specific immunosuppressive agent, cyclosporine. Many advances using other specific immunosuppressive agents have occurred, however, acute and chronic allograft rejection remains one of the leading causes of graft failure and loss. During the past two decades there has been an explosion of knowledge about the immune response to foreign antigens and the immune mechanisms involved in allograft rejection. Both experimental and clinical transplantation and the discovery of new immunosuppressive agents have helped elucidate the cellular and molecular biology of the immune system. It is clear that there is an inseparable link between clinical transplantation and the increased knowledge of these mechanisms.

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Rejection of solid organs occurs as a result of a complex interplay between the innate and adaptive immune systems. T cell-mediated immunity plays an integral role in this process. A very complex, highly coordinated, and tightly regulated process can be simply summarized into the following sequence of events: (i) Recipient T-cells recognize donor-derived ("foreign" or "non-self") antigens via a process called allorecognition; (ii) Recipient T-cells are activated, undergo clonal expansion and differentiation into effector cells; (iii) Effector T-cells migrate to the donor graft, where they promote cell death and eventual allograft rejection. Also key to this process is the CD4 T-cell-mediated activation of B cells, which produce alloantibodies to further mediate allograft rejection.

Immunobiology of Transplantation and Graft Rejection

An in-depth discussion of the immunobiology of transplantation and graft rejection is clearly beyond the scope of this chapter. Therefore, only the major principles and highlights will be reviewed here. For a more in-depth discussion of the immune system in general, the reader is referred to the relevant chapters elsewhere in this textbook. The immune system's response to a donor allograft can be conceptualized as consisting of several distinct phases, including an allorecognition phase; an activation phase; the commitment, proliferation, and differentiation phase; and the effector phase (Fig. 26.1). Thereafter, adaptation occurs in the graft and the host/recipient.

Allorecognition Phase

Following transplantation of a solid organ, cellular movement occurs both in and out of the graft. This cellular traffic is important in the initial steps of bringing donor and recipient cells together. Passenger leukocytes and dendritic cells of the graft migrate to the spleen and other lymphoid tissues in the host, and the host's immune cells migrate to and infiltrate the graft.

Lymphocytes (TCR+ cells) of the recipient come into contact with the MHC antigens of an unrelated donor, and the lack of tolerance for the donor MHC peptide complex results in cellular activation. This recognition can be either direct (antigens on the allogeneic-donor cells) or indirect (donor peptides being presented to the T-cell by host antigen presenting cells, or APCs). In the direct pathway, recipient T-cells recognize intact allo-MHC antigens on the surface of the donor cell. This pathway is thought to be the dominant pathway in the early phase of the alloimmune response and therefore plays a major role in acute allograft rejection [1, 2]. In addition, donor passenger APCs are present in transplanted organs and provide direct stimulation of the recipients T-cells. These APCs also provide necessary secondary costimulatory signals for full T-cell activation.

Indirect recognition results from the presentation of donor MHC peptides in self-MHC class II grooves by recipient APCs to T-cells, and the differences in the amino acid sequences of the donor MHC molecule are recognized, followed by T-cell activation. It has been shown in mouse experiments that mutation of just one amino acid in key sites on the α-helix of the hypervariable regions of the MHC molecule can induce T-cell activation and proliferation. The indirect mechanism clearly plays a significant role in the activation of CD4+ T-helper cells (Th) and therefore is important in initiating help for both an antibody response and the cytotoxic T-cell (Tc), cell-mediated response to foreign MHC molecules. The indirect pathway is an important mechanism in both acute and chronic allograft rejection [3–5].

T-cell Activation Phase

The steps in T-cell activation leading to full commitment of the T-cell with subsequent differentiation and proliferation include the interaction of membrane receptors, membrane to cytoplasm signaling, signal transduction pathways linking the cytoplasm to the nucleus, signals to invoke gene transcription, and production of gene protein products such as cytokines, followed by the interaction of these excreted cytokines with their receptors (Fig. 26.2).

The T-cell receptor (TCR) complex consists of the TCR and the CD3 molecule. To achieve activation, the TCR complex must engage the MHC:peptide complex on the APC, and cross-link by either CD4 (in case of Th cells) or CD8 molecule (in case of Tc cells) to its respective binding site on the MHC. It is known that the TCR-MHC:peptide interactions are short lived and have low affinity and that without this cross-linking of CD4 or CD8, activation likely rarely occurs. Following binding of the TCR, a conformational change occurs which activates the CD3 complex and in turn activates an associated tyrosine kinase. Similarly, cross-linking of CD4 or CD8 results in the activation of an associated tyrosine kinase. In addition, other second signal interactions (costimulation) need to occur at the cell surface to achieve full recognition and activation. Several adhesion molecules play an important role in engaging the T-cell to the APC (non-antigen dependent) to promote the TCR-MHC:peptide interaction. This is particularly true for the naïve T-cell. The adhesion ligand-receptor pairs on the T-cell/APC that appear to be important include ICAM-1-LFA-1 and VLA-4-VCAM-1. Other key second signals in the ligand-receptor pairs with costimulatory functions include CD2-LFA3, CD28-B7, and CD40-CD154 [6, 7].

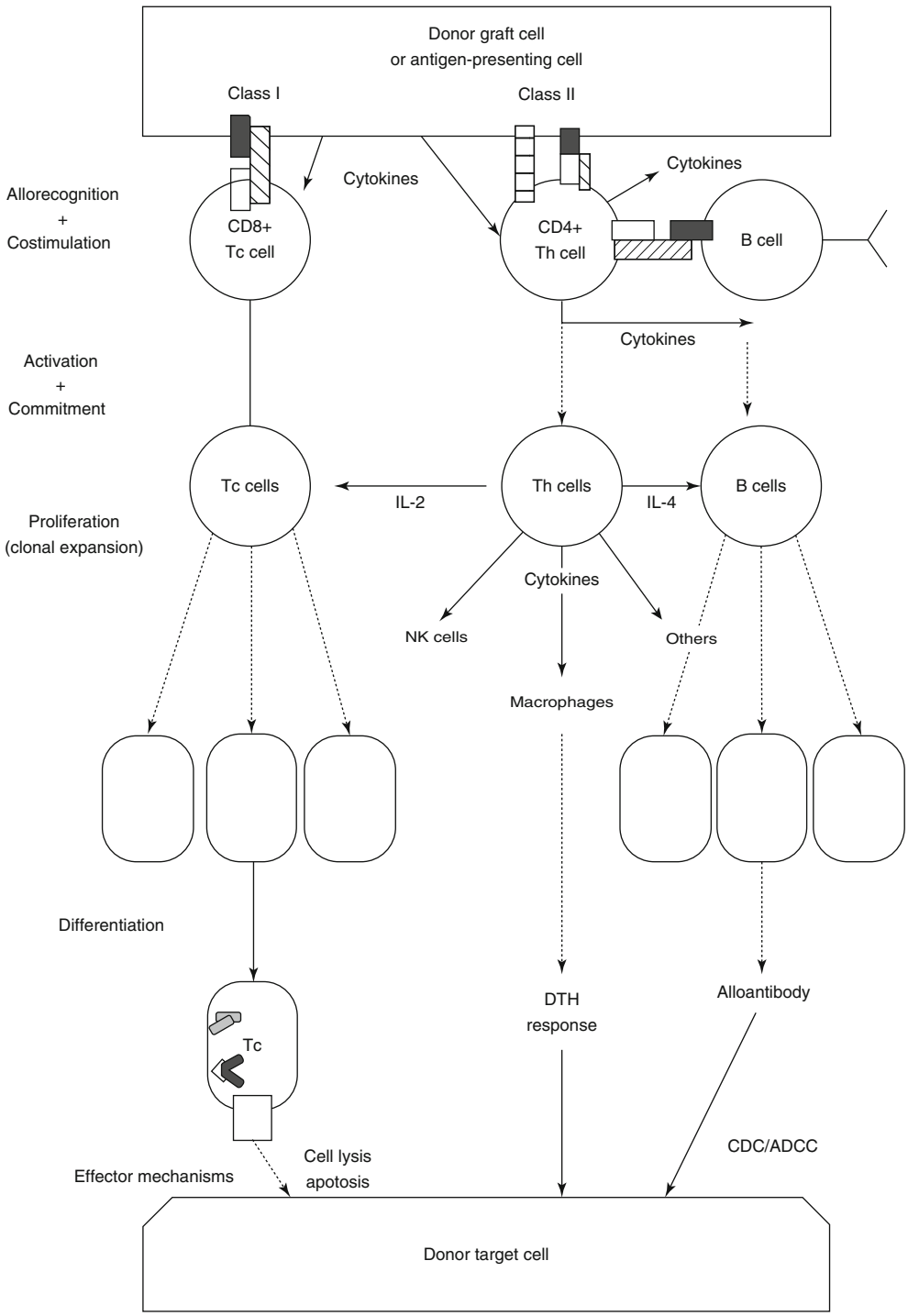

Fig. 26.1 Schematic is a representation of the events that occur during allograft rejection. The immune response to alloantigen can be divided into several phases: An allorecognition and costimulation phase, activation and commitment phase, a proliferation and clonal expansion phase, a differentiation phase and an effector phase. Please refer to the text for further detail (*Th* T helper cell, *Tc* T cytotoxic cell, *NK* natural killer cell, *DTH* delayed type hypersensitivity, *CDC* complement dependent cytotoxicity, *ADCC* antibody dependent cell mediated cytotoxicity)

It has been demonstrated that T-cell/APC interactions void of B7 activation of its ligand CD28 renders the T-cell anergic to that specific antigen [8]. The CD28 molecule also is associated with a tyrosine kinase, which is activated following ligand binding. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) also binds B7 and provides an inhibitory signal. CTLA4 is expressed only on the cell surface of activated T-cells and thereby appears to provide a down regulation function to the immune response [9]. This makes manipulation of the CD28-B7 interaction an attractive target for therapeutic purposes. CTLA4 appears by its function to block CD28 activation and therefore reduce the rejection response. CTLA4 Ig has been produced and binds B7 and thus inhibits CD28 binding. In vitro this results in T-cell anergy. Clinical trials in human transplantation using CTLA4 Ig are ongoing (e.g. abatacept, belatacept) [10].

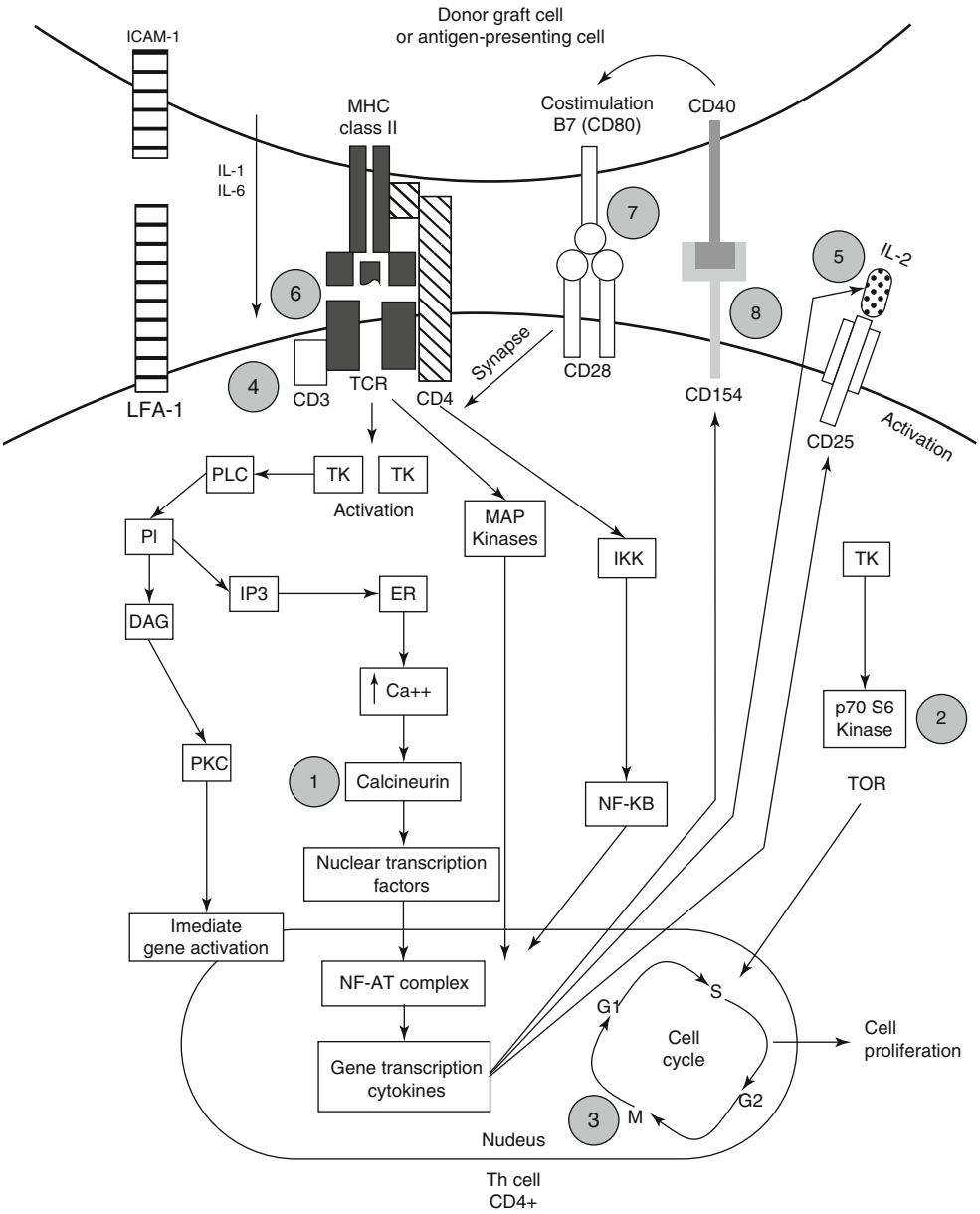

Fig. 26.2 Schematic representation of the crucial events of allorecognition and T-cell activation. Key T-cell and donor cell or APC interactions are depicted. The signal transduction pathways following TCR complex engagement, leading to activation and transcription of cytokine genes is outlined. Refer to the text for a detailed description of events. (*TK* tyrosine kinase, *PLC* phospholipase C, *PI* phosphatidyl inositol, *IP3* inositol triphosphate, *DAG* diacyl glycerol, *PKC* protein kinase C, *ER* endoplasmic reticulum, *NF* nuclear transcription factor, *TOR* target of rapamycin). The sites of action for several immuno-suppressive agents are shown by the *numbered circles*: (*1*) Calcineurin inhibitors CyA and tacrolimus, (*2*) Sirolimus and Everolimus, (*3*) Azathioprine and Mycophenolate mofetil, (*4*) OKT3 monoclonal antibody, (*5*) Basiliximab and Daclizumab (anti-CD25 antibody), (*6*) ATGAM and Thymoglobulin, (*7*) anti-CD28 antibody and CTLA4Ig, (*8*) anti-CD154 antibody

CD40 is expressed on B-cells and APCs including dendritic cells. CD154 is expressed early on activated T-cells. Their binding is critical in providing T-cell help for B-cell Ig production. CD 40 is also expressed on human vascular endothelial cells, smooth muscle cells, and human macrophages. Both CD40 and CD154 are co-expressed in acute cardiac allograft rejection in mice and humans [11, 12]. There is interest in the potential use of monoclonal antibodies directed against CD154 as a therapeutic modality in the treatment and prevention of rejection. However, while studies in nonhuman primates have been reasonably promising, there is a concern for significant thromboembolic complications with this particular drug, as CD154 is expressed on human platelets, but not mouse platelets [10].

Reciprocal *talk* between the T-cell and its surroundings (i.e., the APC) in the form of cytokine stimulation plays a role in strengthening the adhesion between the two cells and in achieving full activation. This reciprocal communication between cells is essential for a strong and complete activation of specific clones of Th cells with a high-affinity response to the alloantigen. In addition, adhesion molecule interactions (selectins and integrins) play a significant role in cellular trafficking by allowing the lymphocytes to sample their environment and take appropriate actions, that is, activation or migration to specific sites [13, 14].

Following TCR-MHC:peptide binding and the other interactions described above, tyrosine kinases are activated. In turn these activate many pathways and components of the T-cell

activation process: G-proteins, phospholipase C (PLC-γ1), phosphatidyl inositol (PI) kinase, and other protein kinases. Approximately 1 h after initiation of TCR binding, mRNA for IL-2 and other cytokines can be found. Tyrosine kinase activation leads to phosphorylation of PLC-γ1. This enzyme lyses membrane phospholipid, PI-releasing diacylglycerol (DAG), and inositol triphosphate (IP3). IP3 binds to receptors on the endoplasmic reticulum and releases intracellular calcium. This in turn activates a number of calcium-dependent enzymes. One such enzyme is calcineurin, which is a serine phosphatase, and is calcium and calmodulin dependent. The other pathway involves DAG-activating PKC. PKC may initiate transcription of genes encoding transcription factors for cytokine genes. Calcineurin activates cytoplasmic nuclear transcription factor (NF-ATc), which when combined with other regulatory factors such as NF-ATn, triggers transcription of cytokine genes (such as IL-2 and others), leading to cytokine synthesis and secretion [15]. Calcineurin is the target of both cyclosporine and tacrolimus. Following the binding of cyclophilin (for cyclosporine) and FK506 Binding Protein (FKBP) (for tacrolimus), the complex inhibits the phosphatase activity of calcineurin [16].

Using a self-stimulatory circuit the newly synthesized cytokines such as IL-2 are secreted and engage their own receptor on the T-cell. IL-2R is not constitutively expressed on resting T-cells, but is induced on T-cell activation. IL-2R and many other receptors are associated with tyrosine kinases and when activated trigger another signal transduction pathway that at present is poorly understood. The p70/S6 kinase appears to be important in the IL-2R signal transduction pathway. Other proteins or kinases may also be important in the pathway. Following p70/S6 kinase activation, further direct and/or indirect steps occur to activate nuclear factors (perhaps NFκB) which initiate cell proliferation by permitting the cell to go from G1 to S phase. The pathway prior to activation of nuclear factors is blocked by the immunosuppressive drug rapamycin. It appears that the rapamycin/FKBP complex blocks the activation of p70 S6 kinase [17]. Following stimulation of the cytokine/receptor activation pathway, the cell becomes committed and will proliferate and differentiate to exhibit its various effector functions. NFκB is an important nuclear transcription factor which is activated by several signals, including TNF, IL-1, and LPS and through TCR activation. NFκB enters the nucleus and binds its specific binding site. Transcription of a number of genes including MHC class I, Ig, and IL-2 then occurs [18]. Corticosteroid therapy interferes with this pathway [19].

Commitment, Proliferation, and Differentiation Phase

Following activation of T-cells, specifically CD4+ Th cells, a sequence of events occurs that results in clonal expansion and differentiation in a number of lymphocyte populations. Activated Th cells can influence many different cell types, including APCs, macrophages, hemopoetic progenitor cells, mast cells, eosinophils, B-cells, Tc cells, other T-cells, and NK cells. It has been demonstrated that many of these changes occur in the graft as opposed to the lymphoid tissues of the recipient. There exists a complex network of positive and negative regulation to guide the cell populations to their eventual phenotype. There are three major pathways of differentiation that lead to the effector mechanisms relevant to transplantation; the CD4 T-cell-dependent alloantibody response, the Tc response by CD8 T-cells, and the DTH response that is Th-cell dependent. Once the cells have differentiated into effector T-cells, any encounter with the specific alloantigen leads to the effector actions without the need for costimulation signals.

Although most cytokines function within an immunologic microenvironment, some have direct systemic effects in response to injury (infection or rejection), such as fever, malaise, myalgia, and cachexia. The prototype cytokine is IL-2, which is the predominant cytokine secreted by Th cells and plays a key role in allograft rejection. IL-2 induces T-cell growth in an autocrine and paracrine fashion. Following activation of CD4+ Th cells, IL-2 binds with its receptor on both Th and CD8+ Tc cells and induces clonal expansion. IL-2 also enhances growth and differentiation of B-cells, macrophages, and NK cells.

IFNγ, secreted by activated Th cells, has many actions, including (i) viral inhibition; (ii) activation of macrophages leading to enhanced expression of IgG receptors and thus increased immune complex clearance, increased phagocytosis, and antibody-dependent cellular cytotoxicity; and (iii) enhancement of MHC class I and II expression on a wide range of cell types. In addition, IFNγ can increase NK cell activity and cause B-cells to undergo terminal maturation and isotype switching to IgG2. IL-4, previously known as B-cell growth factor, is secreted by activated Th cells and acts as a costimulant for B-cell proliferation. IL-4 may also act as a growth stimulator for Th and Tc cells. IL-6 has a broad range of effects. It plays a role in the initial activation of naïve Th cells and has significant hematopoietic effects. Growth and terminal differentiation of B-cells with increased production of IgG, IgM, and IgA are supported by IL-6. In addition, IL-6 has several systemic inflammatory effects similar to IL-1. IL-10 is produced by Th cells and enhances B-cell viability and induces class II MHC expression on B-cells. IL-10 also exerts regulatory effects on T-cells. IL-10 inhibits some APC functions and inhibits IFNγ production by T-cells. TNFα is predominately secreted by activated macrophages and less by T-cells and NK cells, whereas TNFβ is produced only by activated T-cells. TNFα induces multiple systemic effects associated with inflammation and chronic illness. It may also up-regulate IL-2R expression on activated T-cells.

Th-cells can be divided into two distinct populations based on their own repertoire of cytokines that mediate different effector functions. Type 1 Th-cells (Th1 cell) produce IL-2 and IFNγ predominantly and induce macrophage activity. This leads to delayed type hypersensitivity (DTH) responses. Type 2 Th-cells (Th2 cell) produce IL-4, IL-5, IL-10, and IL-13 and provide help for B-cell functions. As such, these cells can inhibit T-cell maturation into the Th1 pathway. A switch from Th1 to Th2 expression has been associated with allograft tolerance, however a causal relationship has not been proven. The Th1/Th2 paradigm in allograft rejection and tolerance requires further clarity [20–22].

Effector Phase

From a clinical-pathologic perspective, the characteristic features of transplant rejection are cell injury and dysfunction of the transplanted organ or cell. These features are initially reversible; however, if the process continues without intervention, it results in irreversible changes leading to extensive necrosis of the organ. The effector mechanisms responsible for allograft rejection can be divided into those which are donor allospecific and those which are nonspecific. Donor-specific mechanisms include cell lysis due to cell-mediated cytotoxicity by Tc cells, and cell lysis by antibody-mediated mechanisms. Nonspecific mechanisms include the inflammatory responses that can be viewed as an analog of the DTH response [23].

CD8 T-cell-Mediated Cytotoxicity

Activation, clonal expansion, and differentiation of CD8 Tc cells correlates with the production and expression of cytoplasmic granules containing perforins and serine esterases known as granzymes. The perforins form multimers on the target cell surface creating holes in the cell membrane. The granzymes enter the target cell cytosol through these holes. The exact mechanism of cell lysis and death is not known; however, the perforins, granzymes, and possibly complement play a role. It appears that granzyme B, a serine protease and possibly other unidentified molecules activate the interleukin-1-converting enzyme-like protease (ICE protease) pathway that together results in apoptosis (programmed cell death). In addition the Tc-cell may utilize the FAS pathway which also induces programmed cell death. Cell mediated cytotoxicity is clearly important in acute allograft rejection but may have less of a role in chronic graft rejection [24].

The pathologic or histologic features of acute cellular rejection that are likely attributable to T-cell-mediated cytotoxicity include the injuries to epithelial and endothelial cells. In renal transplantation this consists of a *tubulitis*, small artery *arteritis*, and *endothelialitis* of arterioles. This corresponds to bile duct epithelial injury and portal vein endothelialitis in liver grafts and myocyte necrosis and endothelialitis in heart grafts. The Tc cell attack on the tubule or bile duct epithelium is directed at the basolateral surface where the majority of basal and inducible expression of MHC antigens occurs with greatest density. The attack on the endothelium can occur from either the luminal or antiluminal surface.

DTH Response in Transplant Rejection

Another important consequence of Th-cell activation is the development of a DTH response. The DTH response is a complex phenomenon that is characterized by edema, fibrin accumulation, and infiltration of numerous cells, including T-cells, B-cells, numerous macrophages, and other leukocytes. The DTH is initiated by activated Th cells and is organized and regulated by the TH1 cytokines and pro-inflammatory cytokines (IL-1, IFNγ, and TNF). It is clear that endothelial cells are not passive bystanders in the process, but (i) act as antigen MHC-presenting cells; (ii) respond to soluble cytokines by increasing adhesion molecule expression; (iii) express platelet activating factor and promote thrombosis and fibrin formation; (iv) synthesize nitric oxide, PGI2, endothelin, and thromboxanes and thus play a role in altering vascular tone and blood flow depending on the stimulus provided; and (v) produce several soluble factors such as IL-1, IL-6, IL-8 (chemotractant for neutrophils), and monocyte chemotactic factor. Therefore endothelial cells play a crucial role in the development of inflammation within the graft [25].

Alloantibody Response in Transplant Rejection

Although the role of alloantibody in the hyperacute rejection process, especially against ABO blood group antigens, has been well known for several decades, the role of alloantibody in rejection as a whole has been potentially underestimated. This is becoming clearer in the context of patients with presensitization to MHC antigens. The antibody-associated graft injury may occur through complement-dependent cytotoxicity mechanisms and/or antibody-dependent cell-mediated cytotoxicity mechanisms. There is evidence that antibodies directed against ABO blood group antigens, class I MHC antigens, and endothelial antigens play a role in the hyperacute rejection response. In pre-sensitized recipients, alloantibody to class I or II MHC molecules probably plays a significant role in the clinical rejection known as humoral or vascular rejection, in acute rejection unresponsive to therapy, and in chronic rejection.

Adaptation of the Graft Following Transplantation

Following organ transplantation, the graft is infiltrated with inflammatory cells from the host due to the rejection processes discussed above and also in response to non-immune, nonspecific injury secondary to surgical events, preservation

techniques, and ischemia. The response to nonspecific injury may play a role in the development of chronic rejection through the up-regulation of adhesion molecules and class I and class II MHC molecules. Over the next several weeks and months, if the graft survives, the inflammatory process diminishes and the adhesion molecule and MHC expression returns to normal. The graft's passenger leukocytes, dendritic cells, and other APCs eventually diminish and are replaced by recipient cells, thereby decreasing the overall quantity of antigen presentation.

The induction or development of tolerance to the graft is the ultimate goal in clinical transplantation. Although numerous techniques are available to induce tolerance in experimental transplant models, particularly in small animal (rodent) models and in a more limited fashion in larger animals (swine), these have not yet been successfully applied in the human clinical situation. Tolerance is the long-lasting state of antigen-specific unresponsiveness that is maintained without ongoing immunosuppression. In the transplant setting tolerance must be thought of as negative response to donor antigen as opposed to no response, which would be considered *neglect* or *ignorance*.

General Concepts of Immunosuppression

In clinical transplantation, immunosuppressive agents are used to achieve either complete immunosuppression (in which the goal is to completely inhibit a rate-limiting step in the immune response) or to achieve maintenance immunosuppression (in which the goal is to reduce a rate-limiting step to a level in which a significant immunosuppressive effect occurs without serious immunodeficiency). All immunosuppressive agents can have three effects: an immunosuppressive effect (therapeutic effects), an immunodeficient effect (complications resulting from the therapeutic effect, i.e. infections and cancer), and nonimmune toxic effects (drug-related toxicity to organs or tissues). As a result of these three effects, five general principles of immunosuppressive therapy have been identified and must be considered when clinicians provide these therapies: (i) the nonimmune toxicities are dose limiting; (ii) combination therapy is useful to increase the immunosuppressive effect and potentially decrease the nonimmune toxicity; (iii) the immunosuppressive effect and the immunodeficiency effect are directly related; (iv) the therapeutic index can be viewed as the immunosuppressive effect divided by the non-immune toxic effect; and (v) the desirable agent(s) is an oral preparation(s) with a short half-life.

Since it is known that the human immune response has extensive pleiotropy and redundancy, it is logical to conclude that monotherapy with a single immunosuppressive agent taken to its maximum effect will fall short of achieving effective prophylaxis or treatment of allograft rejection. This in fact has been the experience. It is becoming clear that drug combination therapy with immunosuppressive agents, whose mechanisms of action target different sites of the immune response without overlapping toxicity, is more effective. Thus, when choosing such a drug combination, the clinician must consider the predominant mechanism of allograft rejection in the given clinical situation, the site of action of the immunosuppressive agents being considered, and the toxicities of those agents. In this fashion a combination of drugs with the most optimal therapeutic index can be chosen. It is essential to understand, however, that combination therapies may not decrease or limit the immunodeficiency effects or complications.

It is useful to classify immunosuppressive agents based on their site of action on the allograft immune response. In addition, the drugs can be classified as being specific to one site of action or nonspecific (the agent has multiple sites of action and effects). A list of immunosuppressive agents in clinical use and those in experimental trials and their site of action are shown in Table 26.1. This chapter begins with an overview of the immune system's response to a donor allograft followed by a detailed discussion of the clinically available immunosuppressive agents, their efficacy in transplantation, and the issues pertinent to patients in the PICU.

Drugs that Block the Signal Transduction Pathway of Activation in T Lymphocytes

The immunosuppressive drugs that selectively block signal transduction pathways of activation in T lymphocytes can be grouped into those agents that bind immunophilins and those that do not. The mechanism of action of the cyclosporines, tacrolimus (FK506), and rapamycin are similar in that they bind their respective immunophilins and block activation of T lymphocytes by inhibiting the signal transduction pathway from the cell surface to the nucleus. For these drugs to have an immunosuppressive effect, the binding of the immunophilins is essential. Thus it appears that the drug-immunophilin complex is the transcellular inhibitor and not the drug itself. Immunophilins are a family of cytosolic proteins present in all tissues. These proteins are isomerases that catalyze cis-trans conformations of peptides, allowing them first to fold into their active confirmations and second to be transported to their proper location in the cell. The cyclosporines bind cyclophilin; tacrolimus and rapamycin bind to the FK-binding protein12 (FKBP12). The inhibitory effect of these immunosuppressive agents does not appear to work by inhibiting immunophilins' isomerase activity. Cyclosporines are cyclic polypeptides, and tacrolimus and rapamycin are related to macrolide antibiotics. The biochemical structures of cyclosporine and tacrolimus are different and yet inhibit T-cell activation via the T-cell receptor at the same intracellular step. Rapamycin has a similar

Table 26.1 Immunosuppressive agents classified by site of action on allograft immune response

Drugs that block the signal transduction pathways of activation in T cells	***Drugs that block allorecognition***
Agents that bind immunophilins	Inhibition of antigen presentation
Cyclosporin A[a]	Soluble HLA antigens
Cyclosporin G	Deoxyspergalin (may block antigen processing)
Tacrolimus (FK5O6)[a]	Anti-TCR
Sirolimus (Rapamycin)[a]	Anti-CD4
Drugs that block proliferation and differentiation	Anti-CD28
Antimetabolites	***Drugs that block effector mechanisms***
Azathioprine[a]	Glucocorticoids (have anti-inflammatory effects and decrease delayed type hypersensitivity)[a]
Mycophenolate mofetil[a]	Adhesion molecule antagonists
Leflunamide	Anti-LFA-L
Brequinar sodium	Anti-ICAM-L
Mizoribine	
Methotrexate[a]	
Drugs that block/inhibit activation by interfering with cell surface interactions	
Receptor antagonists	
Atgam (anti-thymocyte globulin)[a]	
Thymoglobulin (anti-thymocyte globulin)[a]	
Alemtuzumab (anti-CD52 monoclonal AB)[a]	
Basiliximab (anti-IL-2R monoclonal AB)[a]	
Daclizumab (anti-IL-2R monoclonal AB)[a]	
OKT4 (anti-CD4 antibody)	
Anti-CD28	
CTLA4 IG (fusion protein)	
Cytokine inhibitors	
Glucocorticoids (IL-L, IL-6, IFN)[a]	
Anti-IL-2	
Anti-IL-L	
Anti-IL-6	
IL-10	

[a]In clinical use; all others experimental

structure to tacrolimus and binds the same immunophilin, yet its inhibitory action is in completely different pathways. Rapamycin inhibits activation via the IL-2 receptor activation pathway (Fig. 26.2). At the present time the mechanism of action which best explains the immunosuppressive effects of these agents is that the drug-immunophilin complexes (cyclosporine-cyclophilin and tacrolimus-FKBP) bind and inhibit the phosphatase action of calcineurin.

Calcineurin is a calcium-stimulated phosphatase that dephosphorylates NF-AT, allowing NF-AT to enter the nucleus, combing with another nuclear transcription factor, and thereby form an active nuclear transcription factor. This activated nuclear factor binds to the IL-2 gene promoter and activates IL-2 gene transcription with subsequent IL-2 production and secretion. By inhibiting calcineurin, these drug-immunophilin complexes inhibit IL-2 gene activation. Since NF-AT is found only in T lymphocytes, it may explain why cyclosporine and tacrolimus appear to be specific for T-cell activation inhibition [16, 26].

When rapamycin binds FKBP12, the complex binds to another protein, designated as target of rapamycin, TOR. Following this binding, inhibition of another kinase (p70/S6 kinase) occurs. Rapamycin inhibits proliferation of T cells stimulated via the IL-2 receptor [17]. The rapamycin-FKBP12 complex does not inhibit calcineurin activity. Rapamycin also has antiproliferative effects in mesenchymal and endothelial cells as well as potent antimicrobial and antimitotic actions, which are attractive features for patients undergoing transplantation for malignancy. In theory, rapamycin effects may be additive with those of cyclosporine, but these effects antagonize or inhibit the actions of tacrolimus. Because rapamycin may potentially bind up all the FKBP12, the calcineurin may remain active despite the presence of tacrolimus. Therefore, it is controversial whether cyclosporine and rapamycin are synergistic agents, whereas tacrolimus and rapamycin may be antagonistic.

Since cyclosporine and tacrolimus both inhibit calcineurin activity, it is not surprising that their toxicity profiles overlap

to a great degree. Their most significant toxicities include nephrotoxicity [27] and neurotoxicity [28]. The pathophysiology of renal dysfunction is thought to be in part due to calcineurin inhibitor-induced renal vasoconstriction of the afferent arteriole. This vasoconstriction is due in part to the activation of the renin-angiotensin system. It is also related to secretion of the potent vasoconstrictor endothelin-1. Endothelin-1 is released in the kidney to regulate vascular tone, renal blood flow, and sodium reabsorption. It can also induce interstitial fibrosis. These mechanisms of afferent arteriole vasoconstriction can lead to ischemia and overproduction of transforming growth factor-β1 (TGF-β1) which can lead to irreversible glomerulosclerosis and tubulointerstitial fibrosis. It has also been suggested that nitric oxide synthase activity is regulated by calcineurin and may be inhibited by tacrolimus and cyclosporine [29–33]. This, in addition to the renin-angiotensin system, may be responsible in part for the hypertension seen in patients treated with either of these agents. Neurological side effects seen with calcineurin inhibitors range from tremor, headaches, and insomnia to more severe side effects such as seizures that are more commonly associated with tacrolimus [34]. The neurotoxic effects are typically managed by dose reduction, or conversion to another agent.

Cyclosporin A

Cyclosporin A (CyA) had been the cornerstone of immunosuppression regimens for clinical organ transplantation for 20 years and is still widely used. Its clinical efficacy is well described [35–42]. CyA is a cyclic peptide derived from the fungus *Tolypocladium inflatum Gams*. It has a selective T-helper cell activation inhibitory action and thus inhibits cell proliferation. CyA decreases the production and secretion of several cytokines, including IL-1, IL-2, IL-4, IFNy and TNFα. In addition, it decreases the expression of the IL-2 receptor on naïve T-helper cells. As a result of this inhibition, CyA inhibits the cytotoxic T-cell responses, humoral immunity, and delayed-type tissue hypersensitivity responses.

Sandimmune® Formulation: Pharmacologic Considerations

During the past 20 years several features of the pharmacokinetics of the Sandimmune® formulation of CyA have been noted [43]. CyA is an extremely lipophilic drug. Following oral administration, it is absorbed predominantly in the duodenum and jejunum. Absorption is slow, incomplete, and unpredictable. The absolute bioavailability may be as low as 5 % or less and as high as 80 or 90 %. Generally, bioavailability varies among different transplant populations, with the mean bioavailability being approximately 30 %. As a result of the variable absorption, variable peak concentrations are achieved (Cmax). With the Sandimmune® formulation, the peak concentration is generally achieved 2–4 h after dosing. Because the drug is fat soluble, its absorption and metabolism are considerably compromised by hepatic, pancreatic, or biliary dysfunction. In addition, concomitant diet and drug administration may have significant influence on the absorption and bioavailability. Patients with malabsorption syndromes and/or decreased bile flow of any cause will have limited absorption. In patients with poor absorption, IV CyA must be administrated to provide adequate immunosuppression. Following an IV dose, CyA has an initial rapid distribution half-life of 1.1 h. Continuous administration of CyA leads to eventual saturation of the peripheral tissue compartment. In the blood compartment, CyA is highly bound to red blood cells and plasma lipoproteins. As much as 60–70 % of the drug will be bound to erythrocytes and approximately 10 % to leukocytes. The remaining drug is distributed within the plasma and bound to lipoproteins. The distribution in the blood compartment is a function of the drug concentration, the hematocrit, the lipoprotein concentration, and the temperature. Low hematocrit levels, for example, will result in higher drug levels in the plasma. Because of the lipophilic nature of CyA, body fat contains the highest concentrations of the drug. Accumulation occurs in the liver, pancreas, lungs, kidneys, adrenal glands, spleen, and lymph nodes. Very low levels are found in brain tissues, suggesting that CyA does not easily cross the blood–brain barrier. As a result of its high lipid solubility, CyA has a large apparent volume of distribution. Children specifically have a higher volume of distribution for this drug compared with adults and have an increased apparent clearance compared with adults. The half-life is between 4 and 6 h.

CyA is predominantly metabolized by the cytochrome P450 3A enzyme system in the liver, and the metabolites and unchanged drug (<1 % of dose given) is excreted in the bile. Cyclosporine and tacrolimus are also substrates for p-glycoprotein, which acts as a counter-transport pump, actively transporting cyclosporine and tacrolimus back into the intestinal lumen. Less than 6 % of the drug is excreted in the urine. Thus enterohepatic recirculation of metabolites but not the parent compound does occur. Over 30 metabolites have been identified, some of which are known to also possess immunosuppressive effects. Since CyA is dependent on the liver for metabolism and excretion, liver disease and bile duct obstruction or cholestasis have a significant impact on both drug absorption and clearance, resulting in potential increased toxicity. For any given dose there is great inter- and intrapatient variability in absorption, bioavailability, trough blood concentration (Ctrough), Cmax, time to peak concentration (Tmax) and area under the drug concentration-time curve (AUC). In addition, there is poor correlation between the dose given and the AUC, Cmax and Ctrough and a poor

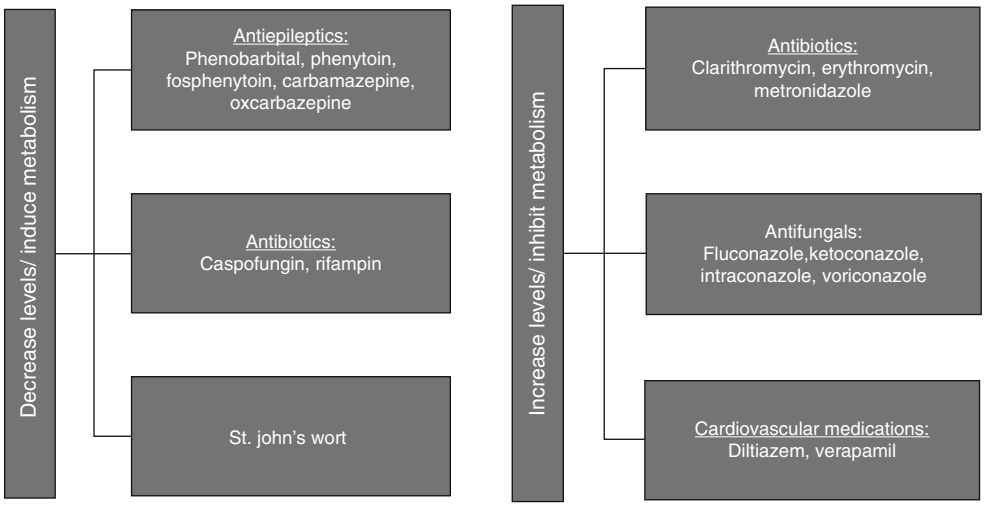

Fig. 26.3 Drugs that increase/ decrease CyA and tacrolimus concentrations

correlation between Ctrough and AUC (measure of total drug exposure) or Cmax [44–46].

CyA has a narrow therapeutic index. Clinicians measure the trough blood concentration of CyA as an indicator of adequate immunosuppression and safety; however, the target ranges used clinically are only best estimates based on clinical experience and not on specific measure of the degree of immunosuppression. There is no reliable and clinically applicable surrogate pharmacodynamic marker except direct histologic analysis of the target tissue at the present time. There may be age dependent differences in the pharmacodynamic effects of CyA, with infants having a significantly increased inhibition of proliferation and IL-2 expression as compared to older age groups at a given CyA blood concentration [47], Clinical experience has revealed that patients with low bioavailability or highly variable absorption and those with low average concentrations of CyA (derived from the drug concentration-time curve) are at increased risk for acute rejection, chronic rejection, and graft failure and loss. Several subpopulations at increased risk include African American patients, children (especially the youngest), liver transplant patients with biliary diversion, and patients with malabsorption syndromes of any cause (e.g., cystic fibrosis). Because of these serious limitations with the Sandimmune formulation, a microemulsion formula (Neoral) has been developed, studied, and in use for several years.

Neoral® Formulation: Pharmacologic Considerations

Studies comparing the pharmacokinetics of the Neoral® and Sandimmune® formulations at equal doses in both adult and pediatric renal and liver transplant patients have revealed (i) improved absorption, absolute and relative bioavailability; (ii) a decreased variability in bioavailability and trough drug concentrations; (iii) a linear dose response; (iv) an improved correlation between Ctrough and drug exposure (AUC); and (v) bile-independent absorption with the Neoral® formulation. In children this improved relative bioavailability with Neoral® is reflected by an increase in the AUC of between 40 and 70 %, by increases in Cmax between 70 and 110 %, and a shorter Tmax (1 ½h). In addition, some studies revealed higher Ctrough by 10–30 %. The greatest changes in bioavailability is in the younger age groups (<5 years) and in those with the poorest absorption of the Sandimmune® formulation. As a result, dosage reduction by as much as 20–50 % is necessary in some children to maintain the Ctrough within a targeted therapeutic range [48, 49]. There are no differences in the metabolites generated from the two formulations since the parent drug is the same, and in the short-term pediatric studies and the 1 year follow up adult studies there had been no significant differences in toxicity profiles between the two formulations. However, there is a suggestion that with improved therapeutic drug monitoring, the use of Neoral® has an improved safety and adverse effect profile [38, 39].

Drug Interactions

Since CyA metabolism occurs via the cytochrome P450 3-A enzyme system in the liver and to a lesser degree in the GI tract, any drug or compound that alters this enzyme system will have an effect on CyA blood concentrations and therefore possibly in immunosuppression or toxicity. Drugs such as phenobarbital or phenytoin that induce the cytochrome P450 enzymes will enhance metabolism and decrease the blood levels. Drugs that inhibit the enzyme system, such as ketoconazole or erythromycin, will decrease the metabolism of CyA and raise the blood levels [46, 50]. Known and suspected drug interactions with CyA are shown in Fig. 26.3 and Table 26.2. Because most transplant patients receive numerous medications, especially in the immediate post transplant phase, careful analysis of their medication list and possible interactions is essential to insure adequate immunosuppression and to avoid unwanted toxicity. Whenever significant

Table 26.2 Adverse effects and toxicities of immunosuppressants

Adverse effects associated with immunosuppressants in children after solid organ transplantation										
	Cortico-steroids	CsA	TAC	AZA	MMF	SIR	ATG	DAC	BAS	ALM
Immunosupression-related adverse effects										
Infection[a]	+	+	+	+	+	+	+++	++	+++	+
Malignancy	+	+	+	++	+	+	+++	+	+++	+
PTLD	+	+	+	+	+	+	+++	+	+++	+
Drug-specific adverse effects										
Growth deficiency	++	?[b]								
Bone-related effects	+++									
Hypertension	++	++	+[c]							
Dyslipidemia	++	++	+[c]			+++				
PTDM	+++	++	++[d]							
Renal failure		+++[e]	+++[f]			?[b]				
Neurologic effects	+++	++[e]	+++[d, f]							
Gingival Hyperplasia		+++								
Acne	+++	++				+				
Hirsutism	+	+++								
Alopecia			++	++						
Hyperkalemia		++	+++[d]							
Hypomagnesemia		++	+++[d]							
GI upset (nausea, diarrhea)	++ (Ulcers)	+	+	++	+++	++	++			+++
Bone marrow suppression				+++	++	++	+++			++
Impaired wound healing	++					++				
Rash						++				++
Infusion-related reactions[e]							+++			+++
Other adverse effects	Fluid retention, myopathy, thin skin, bruising			Hepatotoxicity		Interstitial pneumonitis		Acute hypersensitivity reactions (rare)		Rigors and Hypo-tension w/ infusion

ALM alemtuzumab, *ATG* thymoglobulin, *AZA* azathioprine, *BAS* basiliximab, CsA cyclosporine, *DAC* daclizumab, *GI* gastrointestinal, *MMF* mycophenolate mofetil/mycophenolic acid, *PTDM* post-transplant diabetes mellitus, *PTLD* post-transplant lymphoproliferative disorder, *SIR* sirolimus, *TAC* tacrolimus

\+ Indicates increased risk of adverse effect

++ Indicates significantly increased risk of adverse effect

+++ Indicates studies showing a direct causal relationship with the adverse effect

[a]Infection risk can be dose related

[b]Conflicting reports about an association with the adverse effect

[c]Increased risk exists, but studies appear to indicate a decreased risk compared with cyclosporine

[d]The risk of the adverse effect may be greater compared with cyclosporine

[e]Infusion-related reactions due to cytokine release. Reactions include tachychardia, blood pressure abnormalities, fever, chills, dyspnea, anaphylaxis, and others. It is recommended to premedicate with acetaminophen, diphenhydramine and corticosteroids prior to infusion

[f]Adverse effect is dose related

drug interactions are possible, vigilant therapeutic drug monitoring is warranted. In addition, the effect of the calcineurin inhibitors on the metabolism of the other concomitantly administered drugs must also be assessed.

Dose and Administration

The dose administered to a patient is that needed to achieve and maintain the trough blood concentration (Ctrough) within a therapeutic range. The goal therapeutic range for Ctrough will vary from center to center, may be different for the various types of organ transplants, and will depend on the assay used to measure CyA. It is generally accepted that in the immediate posttransplant period (induction phase), CyA Ctroughs <200 ng/mL would not provide adequate immunosuppression and that Ctroughs >600 ng/mL will place the patient at increased risk for CyA toxicity. When the patient is in the maintenance phase and has good graft function (usually >6 months after transplantation), adequate immunosuppression may be provided by doses achieving Ctrough levels between 100 and 200 ng/mL. Most transplant centers worldwide have adopted the strategy of providing the minimal amount of CyA necessary (Ctrough of between 50 and 100 ng/mL) in order to maintain a healthy allograft over the long term.

CyA can be administrated intravenously or enterally. IV administration is used in the immediate posttransplant period in liver transplant recipients and in other transplant recipients with bowel disease or dysfunction, or for any patient after transplantation who cannot adequately absorb CyA due to malabsorption of any cause (e.g., concurrent infectious diarrheal illness). The starting IV dose is 3–6 mg/kg/day as a continuous infusion over 24 h. This allows the patient to reach a steady state without experiencing high peak concentrations and the associated adverse effects. The IV concentrate (50 mg/mL) is diluted to 1:20–1:100 in 5 % dextrose solution or 0.9 % sodium chloride solution and administered at a peripheral site. Some clinicians use a q12h or q8h regimen with slow infusions over 2–4 h. Patients are converted to oral or enteral CyA as soon as possible after transplantation and the IV drug is discontinued. This conversion may take several days to achieve, and daily Ctrough monitoring is essential during this time.

The oral dose to achieve therapeutic blood level (on a mg/kg basis) will vary from patient to patient and may vary in a given patient over time. A reasonable starting oral dose for children is 8–12 mg/kg/day divided q12h. Daily monitoring of the blood Ctrough is essential. It will take several days for the tissue to become saturated with CyA, after which the blood Ctrough will reach steady state. The therapeutic range is more readily reached with the Neoral® formulation. The dose is adjusted in increments or decrements of 10–20 %. Once the patient has stable Ctrough, they generally need maintenance doses of 8–25 mg/kg/day of the Sandimmune® preparation and doses of 5–15 mg/kg/day of the Neoral® preparation, respectively. Younger children (e.g., those <5 years of age) may need higher doses and/or more frequent dosing (q8h) to achieve and maintain therapeutic blood trough concentrations. Both the Sandimmune® and Neoral® formulations come in liquid solution (100 mg/mL) that can be easily dosed and given to infants and toddlers. The oral solution can be mixed in either orange or apple juice to improve the palatability. Both formulations are also supplied in 25 and 100 mg soft gelatin capsules for the older child and teen.

Drug Monitoring

From the beginning therapeutic drug monitoring (TDM) of CyA was recognized as an essential component of clinical management. CyA trough blood concentration measurements as a means of monitoring have been achieved using several different assays. Concentrations can be measured in whole blood, plasma, or serum. It can be measured using (i) a high-pressure liquid chromatography technique (HPLC) (measures parent drug and metabolites separately); (ii) a polyclonal antibody radioimmunoassay (RIA) technique (measures both parent and metabolite together); (iii) a monoclonal antibody RIA technique (measures parent drug alone); or (iv) a monoclonal fluorescence polarization immunoassay technique (TDx assay), which measures parent drug alone. The HPLC and RIA techniques are rarely used clinically at present because they are labor-intensive assays with a slow turnaround time for results. In the majority of centers the monoclonal TDx assay is used and CyA is measured in whole blood.

During the induction phase trough concentrations are measured daily, with the sample being drawn just prior to the morning dose. Once the patient reaches the desired therapeutic range and is maintained on a stable dose, drug monitoring can be done less frequently (once or twice a week). In general, by 6 months after transplantation, patients may be monitored every other week and after 1 year once a month provided that graft function is normal and stable. A trough blood concentration must be obtained if any of the following are suspected: graft rejection, graft dysfunction due to any cause, diarrhea, malabsorption, changes in metabolism of CyA, an opportunistic infection, an adverse effect such as nephrotoxicity or neurotoxicity, a lymphoproliferative disorder (PTLD), or noncompliance.

Due to the variability of the pharmacokinetics and pharmacodynamics of CyA as described above, studies have shown improved correlation between AUC measurements, dosing, and clinical outcome. Because formal AUC measurements are more cumbersome and time consuming, TDM has evolved over time. Numerous studies have revealed that C2 (CyA concentration at 2 h post dose) monitoring is the best single time point that correlates with the AUC, and is superior over the Ctrough. C2 monitoring has resulted in improved clinical outcomes for long term renal, heart, and liver transplant recipients compared to Ctrough. C2 in the range of 300–600 ng/mL results in a similar calcineurin inhi-

bition compared to higher levels or a Ctrough range of 100–200 ng/mL and is less detrimental to the kidney. In addition C2 monitoring resulted in lower incidence and severity of graft rejection, and a low adverse risk profile compared to Ctrough monitoring. The C2 target range may be different depending upon concomitant immunosuppression utilized, individual pharmacokinetic differences, organ transplanted, drug tolerability, risk of renal toxicity, and time post transplant. C2 monitoring may be helpful in identifying those long term patients who are overexposed to CyA [51–54].

Adverse Effects and Toxicity

The adverse effects associated with CyA can be classified as cosmetic, organ toxicities, and consequences of excessive immunosuppression. The most common and significant adverse effects are outlined in Table 26.2. The adverse effects which are related to CyA drug exposure (concentration) over time are nephrotoxicity, hypertension, hyperlipidemia, gingival hyperplasia, hirsutism, and tremor. Improved TDM as described above can lessen these effects greatly. CyA can also induce hemolytic–uremic syndrome (HUS) and post transplant diabetes mellitus which do not clearly occur in relation to the level of drug exposure. Post transplant lymphoproliferative disorder (PTLD) is not specifically related to CyA as it most often occurs in patients receiving anti-lymphocyte antibody therapy (depleting agents) either as induction therapy or as treatment for steroid resistant rejection [55, 56].

Nephrotoxicity remains the greatest concern with the long term use of CyA. Acute nephrotoxicity is dose dependant and seems to result from a reduction in renal blood flow secondary to afferent arteriolar vasoconstriction. Chronic allograft nephropathy (CAN) remains the second leading cause for renal graft dysfunction and loss in patients with renal transplants. CAN is a chronic fibrotic process and is not clearly dose dependant, however long term high level drug exposure may play a role as evidenced by the improvements seen with dose reduction or withdrawal of calcineurin inhibitors. Mechanisms involved in the development of CAN include activation of the rennin-angiotensin system, increased release of endothelin-1, dysregulation of nitric oxide and NO synthase, upregulation of transforming growth factor-beta1, apoptosis induction, stimulation of inflammatory mediators, and enhanced immunogenecity. Regimens utilizing renal sparing immunosuppressive drugs, or combining CyA with nephroprotective agents such as losartan or pravastatin are being evaluated [57, 58].

In liver transplant patients calcineurin inhibitor therapy is also associated with demonstrable reductions in GFR during the first 3–6 months post transplant, followed by a modest recovery over time; however a chronic decline of 25–35 % in the GFR persists. While some studies have indicated less nephrotoxicity with tacrolimus as compared to CyA, other studies have shown the opposite or no significant difference. These results emphasize the need for careful analysis and consideration of various factors when using calcineurin inhibitors. These include pre-existing renal disease, adjunctive immunosuppressive medications or other drugs with potential renal toxicity, warm ischemia time (in renal transplantation), cardiovascular risk factors, urinary tract infection risk, diabetes mellitus and other metabolic disorders, all which may impact long term renal function [59–63].

Neurotoxicity related to the calcineurin inhibitors has been well described, although the mechanisms are not clearly understood [28, 64]. The incidence of some neurologic adverse event with CyA has been reported in the 10–28 % range. Mild symptoms such as tremors, weakness, peripheral neuropathy, or neuralgia are common and self limited. Severe side effects such as psychoses, hallucinations, blindness, seizures, cerebellar ataxia, or leukoencephalopathy can affect up to 5 % of patients. Liver transplant patients appear to be at greatest risk of neurotoxicity and this may in part be related to underlying pre-existing neurologic disease. Tacrolimus has a very similar neurotoxicity profile to CyA. Patients appear to be at greatest risk with either agent during IV administration. This is likely related to elevated blood concentrations of either drug. Other factors which may play a role in neurotoxicity include advanced liver disease, hypertension, hypocholesterolemia, hypyomagnesemia, and concomitant use of corticosteroids (especially high dose). Reducing the dose or withdrawal of the calcineurin inhibitor results in amelioration of the neurologic symptoms in the majority of patients, however a few patients do experience permanent brain injury or experience a fatal neurologic complication.

A discussion of infectious complications of calcineurin inhibitor based immunosuppression regimens is beyond the scope of this chapter. The incidence of bacterial and fungal infections while substantial is not different between CyA and Tacrolimus based regimens. There appears to be a higher risk of CMV infection and poorer outcomes with hepatitis C virus in patients receiving CyA when compared with Tacrolimus, however this may in part be due to an increased need for adjunctive immunosuppression to treat rejection. Tacrolimus based regimens which include mycophenolate provide excellent rejection prophylaxis, however is associated with an increased incidence of BK virus nephropathy in renal transplant patients. It has yet to be determined if low dose calcineurin inhibitor regimens, early steroid withdrawal, steroid sparing regimens, or calcineurin inhibitor sparing regimens will substantially alter the risks of post transplant infections [65].

Tacrolimus

Tacrolimus (Prograf) is still widely referred to by its experimental designation FK506. Discovered in Japan in 1984, tacrolimus was produced by a strain of *Streptomyces tsukubaensis*. It was first used in clinical trials in patient undergoing liver transplantation at the University of Pittsburgh in 1989 and was licensed for use in clinical liver transplantation in 1994. Tacrolimus inhibits T-cell prolifera-

tive responses in vitro to alloantigen and mitogen stimulation and inhibits cytotoxic T-cell proliferation and differentiation. Its immunosuppressive action occurs through its inhibition of calcineurin as described above (Fig. 26.2). Tacrolimus inhibits the production of cytokines IL-2, IL-3, IL-4, IFNy, TNFα, IL-2R, and granulocyte-macrophage colony-stimulating factor, as well as inhibiting B-cell responses to T cell-dependent antigens, mitogens, and Il-4. Tacrolimus has been shown to be 50–200 times more potent than CyA in achieving these inhibitory effects. This drug does not effect proliferation of T cells once they have been activated, nor does it inhibit IL-10 production by Th2 helper cells. Tacrolimus also inhibits calcium/calmodulin-dependent activities in neutrophils such as neutrophil degranulation and superoxide generation.

In animal studies, tacrolimus inhibits both the T cell-mediated proliferative and cytotoxic responses to alloantigen and the delayed-type hypersensitivity responses, but does not affect antibody-dependent cell-mediated cytotoxicity or natural killer cell activity. Tacrolimus was successful in preventing allograft rejection and treating rejection in a variety of solid organ transplant models and prevents disease in a number of autoimmune disorder models. Clinical trials in liver, renal, and heart transplantation have revealed that tacrolimus is as good as or better than CyA in preventing allograft rejection and is useful in the treatment of rejection that has been unresponsive to steroid and other immunosuppressive therapies [42, 55, 66–69]. It may also be helpful in patients with chronic rejection. In addition to the trend of decreased incidence of rejection, there is a trend to decreased use of monoclonal antibody therapy for treatment of rejection in the tacrolimus group. Tacrolimus has been shown to be particularly useful in prevention of rejection and improving graft and patient survival in small bowel transplantation.

Pharmacologic Considerations

The pharmacokinetics and pharmacodynamics of tacrolimus have been extensively studied [70]. Tacrolimus is a water-insoluble, lipophilic agent that is highly bound to erythrocytes, and as such whole blood measurement is the appropriate method for evaluating pharmacokinetics. The absorption of an oral dose is highly variable. The bioavailability ranges from 14 to 93 %, with a mean of 25 %, and is affected by concomitant administration of food (decreased absorption) and other drugs. The primary site of absorption of tacrolimus is the jejunum, followed by the duodenum, ileum, colon and stomach [71]. Therefore, there is potential for variation in levels, if the enteral route of administration is altered. Oral absorption is not affected by the presence of bile, which is of benefit in patients with biliary diversion or ileus, or in cholestatic patients [72]. Peak blood concentration occurs in 1–3 h post oral administration, and the terminal elimination half-life is 4–41 h (depending on the patient population) with a mean half-life of 12 h (8 h in children). Tacrolimus is highly bound (75–99 %) to erythrocytes and plasma proteins (predominantly albumin and α1-glycoprotein). Tacrolimus can be found in higher concentrations in the liver, lungs, heart, kidney, spleen, pancreas, muscle and brain, but is not detectable in CSF. Tacrolimus can cross the placenta and is found in breast milk.

Tacrolimus is metabolized by the cytochrome P450 system (isoenzymes CYP3A4 and CYP3A5) and is a substrate of P-glycoprotein, which are expressed in the gastrointestinal tract and liver, are involved in oral bioavailability and systemic clearance of calcineurin inhibitors [73].

Less than 1 % of the drug is excreted in the urine, and it is not dialyzable. Some of the metabolites, which are excreted in the bile, also have immunosuppressive effects. Similar to CyA, tacrolimus metabolism and thus blood concentrations are affected by liver dysfunction or failure and any drugs that alter the cytochrome P450 3-A enzyme system or P-glycoprotein activity. In addition, diarrhea can increase tacrolimus levels. Potential theories for this mechanism include inflammation in the intestinal wall, which reduces function of P-glycoprotein (drug efflux pump) and metabolism by CYP450 3A4, increasing TAC bioavailability or a shift in the site of tacrolimus absorption from the duodenum and jejunum to ileum and colon, where metabolism is weaker [74]. Studies utilizing targeted trough drug concentrations would suggest that children need higher doses on a mg/kg basis, and possibly more frequent dosing than adults related to higher volume of distribution and greater clearance than adults [75–78].

Drug Interactions

The drugs that change metabolism and blood concentrations of tacrolimus are identical to those listed for CyA and are shown in Fig. 26.3. In addition, patients receiving both tacrolimus and CyA have an increased risk for severe nephrotoxicity and neurotoxicity; therefore these two agents are not given together, and if the clinician is converting a patient from CyA to tacrolimus, the tacrolimus dose is not initiated until 24–48 h after discontinuation of CyA.

Dose and Administration

As with CyA, tacrolimus dosing is titrated to a targeted drug trough blood concentration (see monitoring below). Tacrolimus can be given intravenously or enterally. In patients with poor renal function prior to transplantation, the administration of tacrolimus may be delayed in an attempt to provide a renal sparing affect. The recommended starting IV dose is 0.01–0.06 mg/kg/day as continuous infusion over 24 h. Because of the high incidence of toxicity with IV administration of tacrolimus, it is not recommended for use. The recommended starting oral dose is 0.15–0.4 mg/kg/day divided q12h. Therapy begins at the lower end of the dosing range and is increased if needed. Daily trough blood concentration monitoring is essential until a stable dose and

concentration are achieved. The oral preparation of tacrolimus is available in a 0.5, 1, and 5 mg capsule. There are no oral solutions commercially available, though extemporaneous preparations can be compounded. However, it should be noted that there are reports of variability in serum levels with the use of these liquid preparations. Some pediatric centers compound lower dose capsules to accommodate patients that need smaller doses.

Drug Monitoring

Since tacrolimus is highly protein and red blood cell bound, it is generally accepted that it is appropriate to measure drug concentrations in whole blood. The drug concentration can be measured using several techniques, including HPLC, a two-step ELISA technique, and the TDx technique. Most centers with transplant programs use the TDx assay on whole blood. The targeted therapeutic range for tacrolimus immediately post transplant will vary with centers and the organ transplanted, and the concomitant immunosuppressive medications utilized. Following liver transplantation it is common to use a targeted Ctrough between 5 and 20 ng/mL. Generally, goal trough levels decrease the further out from transplant, and are typically marinated at around 3–8 ng/mL 1 year after transplant.

In patients with potentially life-threatening viral infections such as cytomegalovirus (CMV) or Epstein-Barr virus (EPV) who have adequate graft function, the goal is to maintain drug levels at the lower end of the therapeutic goal range or to even decrease the goal range. For small bowel transplant recipients, trough drug concentrations in the range of 15–20 ng/mL are often needed to maintain grafts. Unfortunately this is associated with a higher incidence of adverse effects. Similar to CyA, tacrolimus has a narrow therapeutic index and variable pharmacokinetics. Tacrolimus has not undergone the same extensive clinical pharmacokinetic evaluation as has CyA, with respect to AUC or C2 monitoring and the impact on clinical efficacy and toxicity profile.

Adverse Effects and Toxicity

The toxicity profile of tacrolimus is similar to that of CyA except that the degree of toxicities may be different. Nephrotoxicity and neurotoxicity remain the most frequent potentially serious complications and the development of posttransplant lymphoproliferative disorder, especially in children, the most life threatening. Nephrotoxicity with acute renal dysfunction occurs in as many as 33–40 % of patients, with the need for acute dialysis in 10–23 %. In the U.S. multicenter study [66] comparing tacrolimus and CyA there was a higher incidence of nephrotoxicity and neurotoxicity in the tacrolimus group, especially if IV doses were used and the drug trough concentrations were at the high end of the therapeutic range. In addition, patients with nephrotoxicity in the tacrolimus group took longer to recover renal function. In a randomized study in adult liver transplant patients comparing tacrolimus and CyA there was no significant difference in the nephrotoxicity as measured by glomerular filtration rates, serum creatinine, electrolytes, and magnesium concentrations or the incidence of hypertension, diastolic blood pressure, and antihypertensive medication use 1 year after transplantation. This suggests that the nephrotoxic potential of these two agents is very similar. The need for chronic renal dialysis occurs in about 1 % of patients.

Neurotoxicity is more frequent with tacrolimus. Moderate to severe neurotoxicity such as seizures, psychosis, aphasia, coma, and encephalopathy has been reported in 10–32 % of patients. This occurs predominantly in patients receiving IV tacrolimus in whom trough blood concentrations are at the high end of therapeutic range. Mild toxicity such as insomnia, nightmares, tremor, and headaches occur in 30–60 % of patients. These symptoms usually abate with dosage reduction or discontinuation of the drug.

Hypertension may be seen less frequently (30–47 % of patients) with tacrolimus, and this is likely due to lower corticosteroid dose use as compared with CyA regimens. Tacrolimus in adults is associated with a higher rate of hyperglycemia and diabetes compared with CyA when one considers the lower corticosteroid dose in the tacrolimus group. Patients may experience GI toxicity that is manifested as some or all of the following symptoms: diarrhea, anorexia, nausea and vomiting, and poor weight gain. Hyperkalemia and hypomagnesemia can be significant problems in up to 45 % of patients. Potassium-sparing diuretics must be used with caution in patients receiving tacrolimus. Meta-analysis comparing tacrolimus with CyA in renal transplant patients reveals tacrolimus is associated with less acute rejection and less corticosteroid-resistant rejection, less hyperlipidemia and hypertension, but a higher incidence of post-transplant diabetes mellitus requiring insulin therapy, tremors, headache, diarrhea, and dyspepsia. The increased diabetes mellitus appears to be blood concentration dependent [42].

Infectious complications with tacrolimus appear to be similar to CyA based regimens with the exceptions as noted above under CyA. Post-transplantation lymphoproliferative disorder (PTLD) occurs in approximately 8 % of children receiving tacrolimus-based immunosuppression and in as many as 18 % of children younger than 2 years. The occurrence of PTLD in children receiving tacrolimus does not appear to depend on dose or trough level, and is not significantly greater than with CyA based regimens. In general, there is a trend to decreasing mortality and morbidity related to PTLD. This potentially fatal condition points out that tacrolimus and CyA are powerful immunosuppressants and must be used with caution in young children who are at risk for primary infectious with EBV [55, 79, 80]. Further experience with tacrolimus may teach clinicians how to better use this agent to achieve adequate immunosuppression and reduce the toxic adverse effects.

Sirolimus (Rapamycin) and Everolimus

Sirolimus and Everolimus are macrocyclic lactones. Sirolimus is derived from the fungus *S. hydrogroscopicus* [81]. Everolimus is an O-alkylated analog of sirolimus. Both sirolimus and everolimus bind the immunophilin FK506-binding protein 12 (FKBP-12) and inhibit the target of rapamycin (TOR), but do not inhibit calcineurin activity. The resultant complex inhibits the protein kinase TOR, which in turn blocks the downstream pathways that control specific mRNA as required for cell cycle transition from G1 to S phase (Fig. 26.2). This leads to growth arrest of the cell in the G1 phase of the cell cycle. The effects of sirolimus and everolimus thus appear to block proliferation of cells stimulated by cytokines, such as IL-2. Its effects are predominantly on T-cells and B-cells directly. Sirolimus also has the ability to inhibit proliferation of hepatocytes, fibroblasts, and epithelial cells in smooth muscle cells. Inhibition of these mesenchymal cell proliferations may be valuable and exploited in the future to inhibit diseases caused by undesirable cell proliferation. As such these agents may have antineoplastic and arterial protective effects. TOR inhibitors may also have negative effects on wound healing. As such the indications outside of immunosuppression are not yet clearly demonstrated.

Sirolimus and everolimus were initially trialed in combination with cyclosporine. The combination increased nephrotoxicity, induced hemolytic uremic syndrome, and increased the incidence of hypertension [82, 83]. Clinical trials in renal transplantation utilizing a combination of sirolimus and tacrolimus also produced greater incidence of renal dysfunction and hypertension than did the combination of mycophenolate and tacrolimus [84, 85]. This indicates that sirolimus potentiates tacrolimus nephrotoxicity. This had led to immunosuppressive strategies utilizing sirolimus and avoiding the use of calcineurin inhibitors which resulted in improved renal function [86].

In heart transplantation one of the leading causes of graft loss and patient death is cardiac allograft vasculopathy (CAV). CAV is characterized by coronary vascular thickening. Because sirolimus and everolimus have anti-proliferative actions against mesenchymal cells, both have been used in combination with CyA to prevent rejection and decreased the incidence of CAV at 1 year post transplant [87]. In liver transplant populations, the use of sirolimus in combination with tacrolimus has been associated with excessive mortality and graft loss. Many of these patients had evidence of increased incidence of infections at or near the time of death. There is also an increased incidence of hepatic artery thrombosis in these patients. In lung transplant populations, the use of sirolimus has been associated with a number of cases of bronchial and anastomotic dehiscence, which has been mostly fatal. In addition, the side effects of hypertriglyceridemia, hypercholesterolemia, and hypertension have limited its usefulness. As a result, the safety and efficacy of sirolimus as an immunosuppressive therapy in both liver and lung transplant patients and children has not been established. Everolimus is used more in Europe than in North America. Consensus conference guidelines for its use in combination with Neoral and corticosteroids for heart transplantation have been published [88].

Pharmacologic Considerations

The pharmacokinetics of sirolimus and everolimus are similar, however everolimus has a shorter terminal half-life than sirolimus. An oral dose of sirolimus is rapidly absorbed with a mean time to peak concentration of approximately 1 h post ingestion in healthy subjects and approximately 2 h after ingestion in renal transplant patients. The systemic availability of sirolimus is estimated to be approximately 14 %. The bioavailability of sirolimus after administration of a tablet is approximately 27 % higher relative to the oral solution dose. To minimize variability related to food, sirolimus should be consistently taken with or without food. Sirolimus is extensively protein bound, and approximately 97 % bound to serum albumin. Sirolimus and everolimus are extensively metabolized by the cytochrome P-450 3A4 and are P-glycoprotein substrates. They are both metabolized by CYP-3A4 isoenzyme in the intestinal wall and liver and therefore are potentially recycled between the enterocytes in the gut lumen. As a result, the absorption and metabolism of sirolimus and everolimus are influenced by drugs that affect these proteins. Inhibitors of CYP-3A4 and P-GP increase sirolimus and everolimus concentrations, and inducers of these proteins decrease their concentrations. There are seven major metabolites known for sirolimus, and these are detectable in plasma, feces, and urine. Ninety-one percent of the metabolites are recovered from the feces and only approximately 2 % are excreted in the urine. Everolimus forms six weak metabolites that are 80 % excreted in feces and approximately 5 % excreted in urine. Sirolimus and everolimus are the major active compounds, and the metabolites do not appear to have significant immunosuppressive activity.

Following oral dosing, the mean terminal elimination half-life of sirolimus in renal transplant patients is estimated to be approximately 62 h. The mean terminal elimination half-life of everolimus is approximately 50 % that of sirolimus. In pediatric renal transplant recipients, the time to maximum concentration following everolimus oral dosing is approximately 0.8–1.1 h between the ages of 5–18 years. The mean terminal elimination half-life of sirolimus in these pediatric patients is approximately 71 h in the 5–11 year age group and approximately 55 h in the 12–18 year age group. The volume of distribution and clearance of everolimus are lower in pediatric patients from 3 to 16 years of age than

adults, but the half-life is similar to that of adults at about 30 h [89].

Drug Interactions

Similar to cyclosporine and tacrolimus, co-administration of medications which alter the function of CYP-3A4 will have an effect on sirolimus and everolimus concentrations. CyA itself is a substrate and inhibitor of CYP-3A4, and as a result it is recommended that sirolimus should be taken 4 h after administration of cyclosporine. Everolimus AUC also increases considerably with co-administration of cyclosporine [90]. Everolimus Cmin and AUC decreased by 45 % and 48 %, respectively, following a switch from cyclosporine to tacrolimus in a study of six cardiac transplant patients also receiving everolimus [91]. Other agents which inhibit CYP-3A4 include diltiazem, erythromycin, ketoconazole, voriconazole, rifampin, and verapamil. If any of these agents are taken in combination with sirolimus or everolimus, trough concentration monitoring and dosage adjustment is essential.

Dose and Administration

The standard dosing of sirolimus in adults has been between 2 and 5 mg/day with a target goal reaching trough concentrations between 5 and 20 ng/mL. The dosing in children has not been clearly established, however doses in the range of 1 mg/day–3 mg/day have been utilized in order to achieve the target range of trough concentrations. Hepatic impairment increases the mean AUC for sirolimus, and increases the mean termination half-life to approximately 111 h. As a result dosage adjustment is recommended for patients with mild to moderate hepatic impairment. The effects of renal dysfunction on the pharmacokinetics of sirolimus is unknown, however as there is minimal renal excretion of the drug or its metabolites, dosage adjustment is not recommended for renal dysfunction at this time.

Everolimus pediatric dosing data is limited. Studies have used an initial dose of 0.8 mg/m^2/dose twice daily with a maximum single dose of 1.5 mg to maintain serum concentration: 3–6 ng/mL [92]. The reported start time of therapy is variable and has been within 48 h post-transplantation in a multicenter, international trial of 19 pediatric patients while another single center trial including 20 pediatric patients began at 2 weeks after transplantation [93, 94]. In a trial evaluating use for 3 years in pediatric patients <16 years of age, the mean reported dose was 1.53 mg/m^2/day and no major adverse effects were noted [95].

Adverse Effects and Toxicity

The main adverse effects of sirolimus are related to increased susceptibility to infection and possible development of lymphoma and other malignancies, particularly skin cancer. Hyperlipidemia with increased serum cholesterol and triglyceride levels is noted frequently, and may require treatment. The TOR inhibitors have also been associated with thrombocytopenia and leukopenia and this has been consistently observed with sirolimus [84, 85, 95]. These findings do not appear to reflect significant abnormalities. The TOR inhibitors are associated with mean increased incidence of wound complications, including formation of lymphoceles in renal transplant patients. There has been an increased incidence of peri-transplant fluid collections compared to patients not receiving sirolimus. These are likely the result of the antiproliferative properties of the TOR inhibitors on mesenchymal cells. This had led to the recommendation of discontinuing TOR inhibitors when new complications occur. There is a black boxed warning against its use in lung transplant recipients due to the risk of bronchial anastamotic deniscence, but it may be considered farther post-transplant one healing is complete. Overall the incidence of opportunistic infections has been low among patients receiving sirolimus, and in particular the use of sirolimus has been associated with a lower incidence of CMV infection and disease. Sirolimus also carries a warning in liver transplant patients for hepatic artery thrombosis. Most cases of hepatic artery thrombosis occurred within 30 days, so some centers will consider its uses after 30 days post-transport.

Sirolimus Efficacy

The initial clinical trials in adult renal transplant recipients revealed a lower incidence of acute rejection in patients receiving sirolimus and cyclosporin compared to cyclosporin and either azathioprine or placebo. There were no significant differences in graft or patient survival. The sirolimus-treated patients, however, had significantly higher serum creatinine values compared to the azathioprine and placebo comparative groups. This was subsequently determined to be predominantly an effect of the cyclosporin, and therefore led to strategies to either reduce cyclosporin dosing or withdraw cyclosporin altogether [82, 83]. These trials led to improvements in renal function and an acceptable incidence of acute rejection. Pediatric renal transplant trials have not demonstrated superiority utilizing a combination of sirolimus and calcineurin inhibitor compared to a control group. The sirolimus group did have increased risk of renal dysfunction, hyperlipidemia, and urinary tract infections. As a result these studies have not supported the use of sirolimus in combination with calcineurin inhibitor in pediatric renal transplant patients. If sirolimus is to be used in an immunosuppressive protocol in the *de novo* renal transplant patient, it is recommended that cyclosporin be reduced or withdrawn at 2–4 months following transplantation. It is also recommended that sirolimus trough concentrations are monitored and the dose adjusted to achieve target range concentration between 10 and 20 ng/mL.

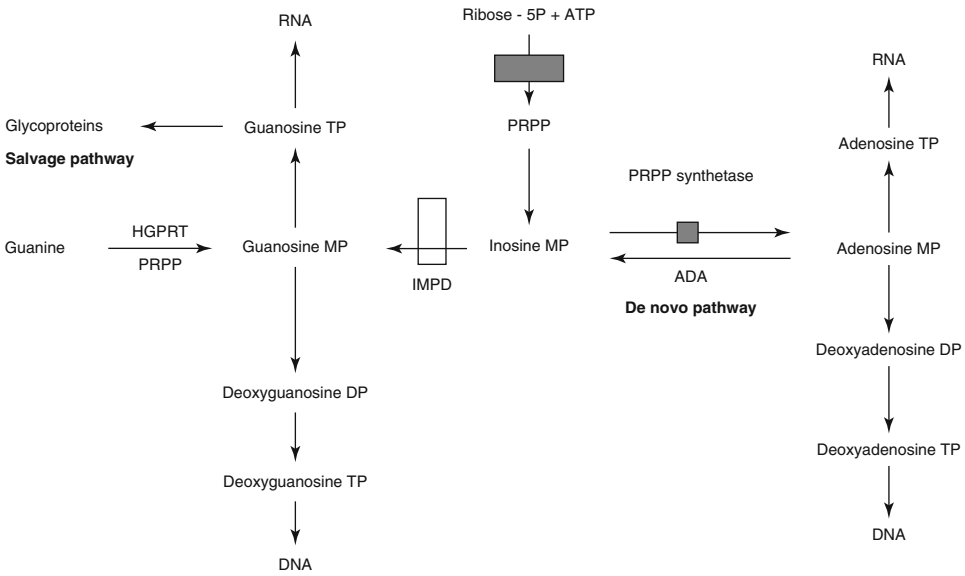

Fig. 26.4 The DeNovo and Salvage pathways of purine synthesis are depicted. The steps which are inhibited by Azathioprine (via thionucleotides) are indicated by the *black boxes*. The step inhibited by Mycophenolic acid is indicated by the *white box*. Please refer to the text for a detailed description (*PRPP* 5-phosphoribosyl 1-pyrophosphate, *IMPD* inosine monophosphate dehydrogenase, *ADA* adenosine deaminase, *HGPRT* hypoxanthine guanine phosphoribosyltransferase)

Everolimus Efficacy

In adult cardiac transplant patients, everolimus was more effective than azathioprine when added to cyclosporine and prednisone for the prevention of allograft rejection [96]. However, a higher rate of serious infection and associated mortality was seen within the first 3 months post-cardiac transplant, so it is not FDA approved for this indication. In adult liver transplant patients, everolimus has been used successfully in combination with reduced dose tacrolimus and corticosteroids after 30 days post transplant. Study arms in which everolimus was used alone were discontinued early due to increased incidence of acute rejection [97]. Everolimus is indicated for the prophylaxis of organ rejection in combination with basiliximab in adult renal transplant patients at low-moderate immunologic risk and concurrently with reduced doses of cyclosporine and corticosteroids [98–100].

Drugs that Block Proliferation and Differentiation

This group of drugs is also referred to as the antimetabolites because they interfere with the metabolism of either purine or pyrimidine nucleotides. This group includes the well-known drug azathioprine and the new drugs mycophenolate mofetil, mizoribine, and leflunamide. The two major pathways of purine synthesis, the *de novo* pathway and the salvage pathway, are shown in Fig. 26.4. These nucleotides are essential for DNA and RNA synthesis and proliferation and play a significant role in other cellular functions such as: (i) the glycosylation of proteins such as the integrins and adhesion molecules; (ii) the production of ATP (cellular energy); (iii) formation of glutamyl transpeptidase, which is important in regulation of G proteins (and thus intracellular signaling); and (iv) adenine nucleotides act as coenzymes in a number of metabolic pathways.

6-mercaptopurine (6-MP) was noted to be effective in inhibiting proliferation of leukemic cells by interfering with purine metabolism and was also an effective immunosuppressant. Subsequently this observation was applied to clinical renal transplantation. Azathioprine is a derivative of 6-MP and is a more powerful immunosuppressant. Azathioprine is converted to 6-MP and an imidazole, both of which have an immunosuppressive effect. The 6-MP is converted to thionucleotides by several steps. These thionucleotides inhibit *de novo* purine synthesis by inhibiting 5-phosphoribosl-1-pyrophosphate (PRPP) formation and the formation of adenylate nucleotides by blocking inosinate dehydrogenase (Fig. 26.4). The reason for greater sensitivity of lymphocytes and neutrophils to azathioprine compared with other rapidly dividing cells is unknown. The salvage pathway is clinically important because one of the enzymes involved in the conversion of the 6-MP to thionucleotides is hypoxanthine guanine phosphoribosyltransferase (HGPRT). After the prolonged use of azathioprine some patients have lymphocytes that mutate and become HGPRT deficient; therefore azathioprine becomes ineffective, placing the patient at risk for rejection.

Mycophenolate mofetil and mizoribine are two agents that inhibit inosine monophosphate dehydrogenase (IMPD) and the *de novo* synthesis of guanosine and deoxyguanosine nucleotides. Mycophenolate mofetil is the morpholinoethyl ester of mycophenolic acid, which is the active inhibitor of IMPD. Mycophenolic acid has a powerful immunosuppressant effect on activated T and B cells in vitro and in vivo. These effects appear to be relatively selective for lymphocytes, which is a favorable feature of this drug. This may be due to the fact that lymphocytes are

more dependent on *de novo* synthesis of guanosine nucleotides. In addition, there are at least two isoforms of IMPD. In resting human neutrophils and lymphocytes, type 1 enzyme is expressed. When T cells are stimulated with mitogen or B cells are transformed with EBV, the type 1 enzymes are still found; however, type 2 enzymes are more strongly expressed. The type 2 isoform appears to be five times more sensitive to mycophenolic acid. This may explain in part the selective inhibition of lymphocyte proliferation with mycophenolic acid [101].

Mizoribine is similar to mycophenolate mofetil except it must be phosphorylated before it can inhibit IMPD. It has no inhibitory action on the early events of T-cell activation. Brequinar is a noncompetitive inhibitor of dihydroorate dehydrogenase, which is an important enzyme in the *de novo* synthesis of pyrimidines. This inhibition causes depletion of thymidine, uridine, and cytosine, resulting in antiproliferative effects. Stimulated lymphocytes have limited pools of pyrimidines and depend on *de novo* pyrimidine synthesis for DNA replication and proliferation to a greater extent than other cells. This selective sensitivity to brequinar theoretically makes this drug useful for its immunosuppressive effects with less potential toxicity. Leflunamide is another dihydroorate dehydrogenase inhibitor and thereby disrupts pyrimidine synthesis. It is approved for use in rheumatoid arthritis and has not been widely used in transplantation. Its active metabolite A771726, has been modified and is in clinical trials for renal transplantation. There is no significant pediatric data at this time with leflunamide [102].

Azathioprine

Azathioprine has been used in clinical transplantation as an adjunctive agent for three decades. It has little effect alone but was used in combination with corticosteroids and other antimetabolite agents for nearly 15 years prior to the introduction of CyA. It is now rarely used as part of triple or dual-drug regimens in combination with steroids and CyA or tacrolimus, especially during the maintenance phase of immunosuppression [103].

Pharmacologic Considerations

Bioavailability from an oral dose of azathioprine is limited to 10–50 %. It undergoes significant first-pass metabolism by hepatic xanthine oxidase to 6-MP, and then a slower conversion that provides a sustained serum level of 6-MP. The half-life of an IV dose of the parent drug is very short due to the rapid uptake and metabolism in the liver. The half life of 6-MP ranges from 1 to 3 h, and is markedly prolonged with renal failure. The unchanged drug and metabolites are excreted in the kidney. It is only slightly dialyzable.

Drug Interactions

The most significant drug interaction for azathioprine is with allopurinol. Allopurinol inhibits xanthine oxidase, which also inactivates 6-MP prior to its conversion to the thionucleotides. As a result, 6-MP levels will rise with greater potential for not only increased immunosuppression but also increased myelotoxicity. If allopurinol is necessary for a patients taking azathioprine, the azathioprine dose must be lowered to 25–33 % of the usual dose. In addition, the azathioprine dose needs to be lowered in patients with significant liver or renal dysfunction or failure. Captopril and enalapril in combination with azathioprine has resulted in severe anemia.

Dose and Administration

The recommended starting oral dose is 3–5 mg/kg/day; however, if azathioprine is used in combination with more than one other agent, it is prudent to start with a smaller dose of between 1 and 3 mg/kg/day given as a single daily dose. The dose can be increased every 4–7 days in increments of 0.5 mg/kg/day until the maximum of 3 mg/kg/day is reached. This lower dose has provided adequate maintenance immunosuppression. If creatinine clearance is <50 mL/min, the dose is reduced by 25 %. The same dosing guidelines can be used for IV administration, however, this is rarely necessary.

Drug Monitoring and Adverse Effects

Azathioprine blood concentrations are not monitored for reasons stated above; however, the end point of toxicity is a reasonable one to help guide dose determination. This is one of these agents in which toxicity limits the dose. In clinical practice the dose is increased to the maximum as outlined above unless there are signs of myelotoxicity (bone marrow suppression) or other signs of toxicity. The total white blood cell count must be kept >3,500 cells/mm^3 and/or the absolute neutrophil count must be kept >1,500 cells/mm^3. If the counts fall below this threshold, discontinuation or significant dose reduction is warranted until the counts are appropriate, followed by reintroduction of azathioprine at only 50 % of the previous dose. Similar adjustments must be made if any of the following occur: thrombocytopenia or anemia, severe diarrhea, nausea, and vomiting and anorexia, or hepatotoxicity. Rarely hypersensitivity reactions can occur and the drug must be discontinued.

Mycophenolate Mofetil

Mycophenolate mofetil has been in use in organ transplant recipients for the treatment and the prevention of rejection for the past decade. Mycophenolate mofetil is a fermentation product of several species of *Penicillium*. Rescue treatment with mycophenolate mofetil of renal, heart, or liver transplant

patients with acute rejection unresponsive to corticosteroids, monoclonal antilymphocyte agents, and CyA and in patients with chronic rejection has been successful. In three randomized studies comparing mycophenolate mofetil with azathioprine or placebo, patients treated with mycophenolate mofetil have a lower incidence of rejection compared with those given azathioprine, and an improved toxicity profile. It has also been evaluated in heart and liver transplantation, pediatric populations, and has largely replaced the use of azathioprine [104–109].

Pharmacologic Considerations

Mycophenolate mofetil is rapidly absorbed following oral administration and has an absolute bioavailability of >90 %. It undergoes rapid metabolism to form mycophenolic acid (MPA), the active metabolite prior to reaching the central circulation. Following oral administration, peak concentrations of mycophenolic acid occur at about 1 h. Mycophenolic acid can be measured in the blood and the AUC appears to be dose related in a linear fashion. In renal transplant patients in the immediately postoperative period the mean AUC and Cmax are reduced by 50 % compared to stable patients several months after transplantation. In liver transplant patients biliary diversion does not appear to alter bioavailability. The presence of food does not appear to reduce the bioavailability by AUC measure, but it does reduce Cmax by as much as 40 %, indicating a probable delay in absorption. Mycophenolic acid is 97 % bound to plasma albumin. None of the usual drugs used in clinical transplantation appears to displace mycophenolic acid from albumin and raise its free fraction. Mycophenolic acid is metabolized in the liver to mycophenolic acid glucuronide. This inactive metabolite is excreted in the urine (93 %) and in the bowel (6 %), where it is converted back into active mycophenolic acid and reabsorbed (enterohepatic recirculation). High concentrations of mycophenolic acid can be found in the bowel. As a result of the enterohepatic recirculation of mycophenolic acid, second peaks can be seen in the drug concentration time profile between 6 and 12 h after dosing, and may contribute as much as 10–60 % of the AUC of MPA. The terminal elimination half-life is 16–18 h. Mycophenolic acid is not readily removed by hemodialysis. High doses (2–4 g/day) are needed in adults to sustain suppression of the alloimmune response. This may be due to the drug's effective conversion into an active metabolite, low binding affinity with IMPD, or extensive plasma protein binding [110–114].

Doses of mycophenolate mofetil from 100 to 3,500 mg have been well tolerated in humans. In adults the responses are dose dependent, with the least rejection episodes occurring in patients receiving at least 2 g/day. Pharmacokinetic data in children are available from one study of renal transplant recipients. In a dose escalation study in which children who received 15 and 23 mg/kg bid, both the AUC and the Cmax were reduced by 50 and 75 %, respectively in children under 6 years of age. There is no clear explanation why bioavailability of this drug is reduced in younger children. Both doses were equally effective at preventing rejection, and the drug was well tolerated. In another study children received 1,200 mg/m^2 body surface area in two divided doses. All patients received CyA and prednisone in addition. The AUC curves of total MPA and free MPA were comparable to adults receiving 2 g/day of mycophenolate mofetil. There is significant intraindividual variability of MPA exposure early post transplant which becomes more stable over time, whereas interindividual variability does not change over time. There are no age and racial differences in mean MPA AUC. The AUC of total MPA increases by as much as 100 % over the first 3–6 months post-transplant and thereafter remains stable. The free MPA AUC remains relatively unchanged. This reflects a negative correlation between the free MPA AUC and GFR in both children and adults. Another factor important in this effect is that corticosteroids induce hepatic glucuronyl transferase activity and renal transplant patients tend to receive high doses early post-transplant and received tapered doses over time. As such, MPA metabolism is greater early on post-transplant [115–118]. Discontinuing corticosteroids increases MPA exposure by about 20 %. CyA has a moderate inhibitory effect on MPA exposure by reducing enterohepatic recirculation, while tacrolimus appears to raise MPA exposure suggesting an inhibition of glucuronidation [119, 120].

Drug Interactions

Magnesium- and aluminum-containing antacids and cholestyramine reduced drug absorption significantly. Antacids may be given but not at the same time. Cholestyramine must not be given since it interferes with the enterohepatic recirculation. Similarly, drugs that alter the gut flora may also change the enterohepatic recirculation of mycophenolate.

Dose and Administration

Oral dosing for adults is reasonably well established. The starting oral dose is 1 g two times a day given in combination with CyA and prednisone. Although patients received 1.5 g two times a day in the studies, there is no proven additional benefit to this dose, and a total of 2 g/day does have a better toxicity profile. Manufacturers give no recommended dosing guidelines for children; however, based on the data in children and the current experience, a starting oral dose of 600 mg/m^2 body surface area two times a day is reasonable. The maximum dose should not exceed 2 g/day. The dose should be taken 1 h before and 2 h after food intake.

Drug Monitoring

Neutropenia and lymphopenia, less frequent with mycophenolate than with azathioprine, may still occur, therefore intermittent evaluation of total white blood cell count and absolute neutrophil count is warranted. If this occurs, the

dosage of mycophenolate must be reduced or discontinued completely. TDM may be beneficial for mycophenolate, since there is a strong correlation between MPA levels and pharmacodynamic parameters and clinical rejection, significant interindividual variability at a fixed dose, the predictive value of MPA AUC and trough concentration for risk of acute rejection, significant drug interactions with mycophenolate, and significant changes in MPA pharmacokinetics over time. The value of TDM of MPA has not been formally evaluated. The target range of exposure for MPA have not been established [121, 122].

Adverse Effects and Toxicity

Mycophenolate mofetil is well tolerated. There have been no reports of significant nephrotoxicity, hepatotoxicity, neurotoxicity, bone marrow suppression, or cardiac toxicity. This drug has been used in the treatment of psoriasis for many years, documenting long-term safety in humans. Leukopenia occurs in about 25 % of adult patients and in 17 % of children. Approximately 30 % of patients do experience difficulty with diarrhea and 10 % with nausea and vomiting. The gastrointestinal side effects may be alleviated by decreasing the dose or reducing the dosing interval (i.e. lower dose more frequently) [123]. An enteric coated formulation is available as an alternative to mycophenolate mofetil.

Mycophenolate mofetil and azathioprine are Pregnancy category D meaning that there is positive evidence of human fetal risk. However, potential benefits may warrant use of drug in pregnant women despite potential risk. There are reports of structural malformations and spontaneous abortions in pregnancies exposed to mycophenolate mofetil. An interaction exists between MMF and oral contraception, so it is recommended to use two forms of contraception 4 weeks prior to starting treatment and 6 weeks after the last treatment dose of mycophenolate or azathioprine.

Leflunamide

Leflunamide is a drug derived from compounds originally synthesized as agriculture herbicides. It is a pro-drug and once it enters the blood is converted to its active form, A77 1726. A77 1726 is very stable; the half-life in rodents is 10–30 h and in humans is variable and can be up to ten times as long. Leflunamide is another dihydroorate dehydrogenase inhibitor and thereby disrupts pyrimidine synthesis. Animal transplant studies have shown excellent graft survival of renal and heart allografts used both alone and in combination with CyA. There appears to be little toxicity with this drug in these models.

Leflunamide has been used in human patients for the treatment of rheumatoid arthritis in Europe for several years with excellent results. At doses of 5, 10 or 25 mg/day there is little significant toxicity reported and the drug appears to be well tolerated. Human clinical trials in transplantation are under way. The attractive feature of this agent is that it appears to have no nephrotoxicity, and yet has good immunosuppressive properties that may allow for its use in combination with low doses of CyA or tacrolimus.

Mizoribine

Mizoribine, a nucleoside antibiotic, was isolated from a fungus in 1974. It is similar to mycophenolate mofetil except it must be phosphorylated before it can inhibit IMPD. It has been used extensively in Japan for the prevention of allograft rejection and in the treatment of some autoimmune conditions. Several randomized and nonrandomized studies from Japan in the 1980s revealed that mizoribine was at least as effective and in some cases provided improved immunosuppression compared with azathioprine, both alone and in conjunction with CyA and steroid-based regimens. In addition, patients treated with mizoribine had significantly fewer problems with bone marrow suppression and hepatotoxicity and fewer infectious complications. It has been associated with gastric irritation and hemorrhagic gastritis. These studies suggest that mizoribine may not only be an effective immunosuppressant, but may offer advantages over azathioprine. Whether or not it would offer any advantage over mycophenolate has yet to be determined. At present mizoribine is not available for clinical use in North America.

Drugs that Block or Inhibit Activation by Interfering with Cell Surface Interactions

The agents that inhibit T cells from activation or full commitment to proliferate can be grouped into (i) cell surface receptor antagonists targeting either molecules of allorecognition and activation, molecules with costimulation function, or molecules with adhesion function; and (ii) cytokine inhibitors, which will blunt important second signals of activation and amplification. These agents are listed in Table 26.1 and their sites of action in the immune response are illustrated in Fig. 26.2. ATGAM® and Thymoglobulin® (both antithymocyte globulins), basiliximab and daclizumab (both monoclonal anti-IL-2R antibodies) and corticosteroids are the only agents listed that are currently licensed and available for clinical use in North America. The other agents listed have undergone preclinical study (many with promising results) and several are in various phases of clinical trial.

Antithymocyte globulins are biologic products produced by immunizing an animal with human thymus tissue. They have been produced in horses, rabbits, and goats. ATGAM® is a polyclonal globulin produced in an equine host. Thymoglobulin® is a purified, pasteurized gamma

immunoglobulin produced by immunizing rabbits with human thymocytes. The antithymocyte globulins, including ATGAM®, have been used in clinical transplantation sine the 1970s and have been shown to be effective at preventing or delaying the onset of rejection in renal, liver, and heart transplant recipients. The polyclonal nature of these products is part of their advantage since they contain multiple antibodies directed at different cell surface molecules on lymphocytes and monocytes, and therefore have the ability to deplete many different immune cells involved in the allograft response. This may account for their success in the pre-CyA era and why they are also more beneficial for rejection prophylaxis in young pediatric liver transplant recipients today. The polyclonal products, however, have the disadvantage of having antibodies directed at surface molecules of other circulating cells such as platelets and red blood cells. Thrombocytopenia and anemia are thus a potential risk. Both ATGAM® and Thymoglobulin® are purified to eliminate these non-antilymphocyte antibodies as much as possible and there is reasonable consistency in the batch-to-batch potency. The other disadvantage of the nonselective nature of the antithymocyte globulins is the potential increase in overimmunosuppression with the resultant development of infectious complications (especially viral infections).

Monoclonal antibodies targeting different molecules involved in the allograft immune response have been developed over the past 15 years to provide specific immunosuppression of T cells. Efforts are now under way to produce clinically useful monoclonal antibodies that may induce specific alloantigen tolerance. In addition to their specificity to lymphocytes, the other advantages of the monoclonal antibodies include the ability to produce them in small animals or in culture systems in vitro (this helps keep the cost down) and the potential to genetically engineer more specificity or to attach cellular toxin that can be delivered in a selective manner. The disadvantages of the current monoclonal antibodies include the potential for host antibody production against the murine (foreign) protein (human antimouse antibody, or HAMA) and the development of the cytokine release syndrome (often referred to as the *first-dose syndrome*). These two phenomena will be discussed more below.

Monoclonal antibodies targeting activated T lymphocytes are anti-IL-2 receptor antibodies (anti-Tac and anti-CD25); they have the theoretical advantage of only reacting with lymphocytes that have been activated by alloantigens. Resting lymphocytes and those active against infectious agents do not express IL-2 receptors and therefore would be spared. These antibodies are now in clinical use and continue to be studied. They have been used for induction prophylactic therapy and for the treatment of rejection in all solid organ transplants with good success.

Anti-CD4 monoclonal antibodies are attractive since the CD4 molecule plays a significant role in allorecognition and costimulation of T-helper cells. In vivo animal experiments have shown that some anti-CD4 antibodies can induce long-lasting specific tolerance if given at the time of transplant. There are many different anti-CD4 antibodies with different effects. Medications that are in testing include clenoliximab, keliximab, priliximab, and zanolimumab. Some disturb allorecognition and induce tolerance, whereas others deplete the peripheral circulation of T cells without inducing tolerance.

The adhesion molecules play an important role in the cell-to-cell interactions during the activation and in the effector mechanisms of the immune response. Antibodies directed at the various adhesion molecules such as intercellular adhesion molecule-1 (1CAM-1) or leukocyte function-associated antigen-1 (LFA-1) have profound immunosuppressive effects. Several experimental transplant models have shown improved graft survival following the administration of anti-1CAM-1 antibody or anti-LFA-1 antibody.

ATGAM

A polyclonal antilymphocyte equine product, ATGAM® has been successful in preventing graft rejection in combination with corticosteroids, CyA, and azathioprine in adults and children in all solid organ transplants and has been used to treat and prevent graft-vs-host disease (GVHD) in bone marrow recipients [124, 125]. ATGAM® depletes the lymphocytes from the peripheral circulation, lymph nodes, and spleen. The mechanism responsible for this depletion is poorly understood but is believed to involve antigen-dependent cell-mediated lysis and complement-dependent cell lysis. When used for rejection prophylaxis in the induction phase after transplantation, ATGAM® is given with corticosteroids and the introduction of CyA or tacrolimus may be delayed. Azathioprine or mycophenolate may or may not be used in these regimens. ATGAM® is not continued for longer than 7 days in this clinical situation. This sequential strategy of immunosuppression also provides a renal-sparing effect in that the potentially nephrotoxic drugs such as CyA or tacrolimus are not given until adequate renal function is established. ATGAM® may also be used to treat acute rejection if high-dose steroid therapy has failed.

Pharmacologic Considerations

Measurements of horse IgG antibody following a single dose of ATGAM® revealed that this product has a half-life of approximately 5–6 days. Prior to administration an intradermal test dose injection of 0.1 mL of a 1:1,000 dilution of ATGAM® is recommended. If after 60 min there is no reaction (wheal or erythema), it is safe to administer the drug. If a positive response occurs (>10 mm), alternate therapy must be considered. A systemic reaction no matter how mild is a contraindication to further use of ATGAM®.

Dose and Administration

ATGAM must be diluted in 0.9 % sodium chloride solution and not in dextrose solution since low sodium concentrations may lead to precipitation. The recommended dose in adults is 10–30 mg/kg/day. This dose can be given once a day or divided into twice-daily doses. The duration of therapy of 7–14 days is at the discretion of the clinicians. In children the recommended dose is 15–25 mg/kg/day; however, young children have received up to 45 mg/kg/day to achieve the desired lymphocyte depletion without serious adverse effects. It is accepted to initiate ATGAM at 7.5 mg/kg/dose twice daily and adjust the dose daily to achieve a targeted absolute lymphocyte count until a maximum dose of 45 mg/kg/day, or side effects occur. Children older than 5 years can achieve adequate counts at 15 mg/kg/day, but younger children may need 20–25 mg/kg/day or more. ATGAM is infused in a central venous catheter slowly over 6 h. Pretreatment with Solu-Medrol (1 mg/kg/day), diphenhydramine (1 mg/kg), and acetaminophen (10–15 mg/kg) 30 min prior to the infusion helps prevent chills, fever, erythema, and itching that often accompany the infusion.

Drug Monitoring

The total white blood count and the absolute lymphocyte count are monitored to determine the end point of ATGAM therapy. The importance of matching the therapy to lymphocyte depletion by keeping the absolute lymphocyte count to <10 % of pretreatment levels was shown in the early 1980s. This has resulted in the recommendation to keep lymphocyte counts <500 cells/μl. It has been shown that T-cell subsets (CD3, CD4, and CD8 cells) are all equally depressed in children following ATGAM administration. Children younger than 5 years may require larger doses of ATGAM to achieve this same level of depletion, possibly due to a more rapid repopulation of their peripheral circulation than occurs in older children. In addition, monitoring is essential to diagnosis any signs of adverse reactions. During the infusion of the first two doses the patient's vital signs, temperature, respiratory effort, and mental status are monitored at least every 15 min for the first 2 h and every half hour until completion.

Adverse Effects and Toxicity

The most common adverse reaction to ATGAM® is the onset of chills and fever, probably due to the release of endogenous pyrogens from monocytes and neutrophils as they are damaged by the antibodies. The cytokine release syndrome has not been studied with ATGAM® administration; however, it is certainly a possible mechanism. Fever is maximal on the first days of administration and generally resolves thereafter. Itching and erythema may occur from histamine release. Serum sickness, anaphylaxis, and hemolysis are rare complications. Thrombocytopenia can occur in as much as 40 % of patients over several days; however, rarely does the platelet count fall below 50,000/μl or the drug have to be discontinued.

Thymoglobulin

Thymoglobulin® is a purified, pasteurized gamma immunoglobulin produced by immunizing rabbits with human thymocytes. This polyclonal product contains cytotoxic antibodies directed against multiple antigens (T-cell markers) on human T lymphocytes. Mechanisms of action for Thymoglobulin include T-cell clearance from the circulation and modulation of T-cell activation, homing mechanisms and cytotoxic activities. When used as an induction agent, Thymoglobulin® produces a significant and durable lymphopenia which may last up to 1 year [124]. When compared directly to ATGAM®, Thymoglobulin® produces significantly greater lymphopenia, and therefore is often favored over the horse polyclonal anti-thymocyte globulins. Compared to ATGAM®, however, Thymoglobulin® is also associated with a higher incidence of leukopenia and is only slightly more effective than ATGAM in both preventing and treating acute graft rejection [124, 126, 127]. Thymoglobulin® is indicated for the treatment of acute graft rejection in conjunction with concomitant standard immunosuppression, and also is utilized for induction therapy at some centers.

Pharmacologic Considerations

Following even a single intravenous dose of Thymoglobulin®, a significant decline in T-cell counts is measurable. The half-life of Thymoglobulin® is approximately 2–3 days. Thymoglobulin® is eliminated by opsonization and phagocytosis. Following multiple infusions, the elimination half-life is highly variable with a reported range of 13–38 days. Some patients may have measurable Thymoglobulin® levels at 1–3 months post-treatment [128].

Drug Interactions

Thymoglobulin® is usually administered concomitantly with standard immunosuppressive medications, and this may predispose patients to over-immunosuppression. As a result, most transplant centers decrease the maintenance immunosuppression therapy during the period of antibody therapy. It is recommended to discontinue or significantly decrease concomitant steroids, and decrease the blood concentration of CyA or tacrolimus by 50 %, and decrease the mycophenolate mofetil dose by 50 % while administering Thymoglobulin®. Due to the risk of over-immunosuppression, antiviral prophylaxis is recommended during Thymoglobulin treatment, and continued for up to 3 months, in addition to *Pneumocystis jiroveci* prophylaxis for up to 6 months.

Dose and Administration

Thymoglobulin is a freeze-dried product for intravenous administration following reconstitution with sterile water. The reconstituted product contains 5 mg of Thymoglobulin® per milliliter. The standard Thymoglobulin® dose is 1.5 mg/kg per day, infused once a day through a central venous catheter. The first dose is administered over 6 h, and subsequent doses may be administered over 4 h. One hour prior to infusion it is recommended to utilize a dose of corticosteroid, acetaminophen and/or an antihistamine such as diphennydramine. The course of therapy is generally between 3 and 10 days for induction therapy, and between 7 and 14 days for treatment of acute graft rejection. Monitoring of T-cell counts to assess the level of T-cell depletion and efficacy of the drug is recommended. Monitoring total white blood cell count and platelet count is also recommended to monitor for adverse effects. Thymoglobulin® dose is adjusted by a decrease in the dose by 50 % if the platelet count is less than 75,000 or the white blood cell count is less than 3,000. If the platelet count drops less than 50,000, or the white blood cell count drops to less than 2,000, it is recommended to discontinue Thymoglobulin® until the counts recover. Graft function should also be monitored daily to evaluate efficacy of therapy.

Adverse Effects and Toxicity

Thymoglobulin infusion produces fever and chills in approximately 50 % of patients. To minimize these first dose effects, the first dose is infused over a minimum of 6 h through a central venous catheter. Premedication with corticosteroids, acetaminophen, and/or an antihistamine may reduce the reaction incidence and intensity. Anaphylaxis has been reported with Thymoglobulin® infusion, but is rare. Leukopenia is common, thrombocytopenia occurs in approximately 35 % of patients, and anemia occurs in less than 10 % of patients. Prolonged use or overdosage of Thymoglobulin® in association with other immunosuppressive agents renders the patient at an increased risk for severe infections including CMV, and EBV related post-transplant lymphoproliferative disease or other malignancies. Appropriate antiviral prophylaxis (ganciclovir) and appropriate monitoring during Thymoglobulin® use is recommended. The development of anti-rabbit (anti-thymoglobulin) antibodies following a course of therapy has not been extensively evaluated, however preliminary data suggest that the incidence of development of such antibodies is low [129].

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52 cell surface glycoproteins. Alemtuzumab binds to CD52 which is found on the surface of essentially all B and T lymphocytes, a majority of monocytes, macrophages, and NK cells, and a subpopulation of granulocytes. It has been used extensively in lymphoid malignancies, autoimmune diseases, and organ transplantation with some of this data being in children [130, 131].

Pharmacologic Considerations

CD52 is the most prevalent surface glycoprotein found on lymphocytes. After systemic administration, it results in prolonged T cell depletion from circulation despite its half-life of 12 days. T-cells generally will recover to 50 % of baseline at 36 months. Other cell lines with CD52 receptors are affected to a lesser extent, and monocyte recovery can occur at 3 months and B-cell recovery can be seen at 12 months. The depletion of lymphocytes in lymph nodes takes 3–5 days compared to <1 h for peripheral lymphocytes. Although alemtuzumab isn't approved for solid organ transplantation, it ability to deplete lymphocytes and positive results from studies in renal and other solid organ transplant patients have led to its use in these populations [132].

Dose and Administration

The alemtuzumab dose used in adult renal transplant induction is 20 mg or 0.3 mg/kg/day for a total of two doses with one dose administered on the day of transplant and the second dose the following day or day 4 post-operatively. Methylprednisolone was administered prior to the first and/or second dose [133–135].

Tzakis et al. reported use of alemtuzumab with tacrolimus for liver and intestinal transplantation in 11 pediatric intestinal recipients and adult intestinal and liver recipients. In this series, alemtuzumab was administered at 0.3 mg/kg IV for four doses given preoperatively, immediately post-operatively, then on post-op days 3 and 7 [136].

Tan et al. analyzed 42 pediatric living donor kidney transplantations that were treated with alemtuzumab pre-treatment and tacrolimus monotherapy. Their protocol uses alemtuzumab 0.4–0.5 mg/kg intravenously given once either the evening before or in the operating room after anesthesia induction. Patients were pre-treated with 10–15 mg/kg of methylprednisolone [132].

For B-cell chronic lymphocytic leukemia, package labeling recommends to pre-medicate with diphenhydramine and acetaminophen 30 min prior to each infusion and utilize *Pneumocystis jiroveci* and viral prophylaxis for at least 2 months after completion of alemtuzumab or until the CD4+ count is at least 200 cells/mcL, whichever occurs later [137].

Adverse Effects and Toxicity

As with all antibody medications, there is a risk of initial reaction with alemtuzumab administration. The administration of steroids, diphenhydramine, and acetaminophen prior to infusion can decrease this risk. There seems to be less risk than with other antibody therapies for infection and post-transplantation lymphoproliferative disease despite the profound and long-lasting T-cell depletion that it causes [138].

Alemtuzumab Efficacy

Alemtuzumab is FDA approved and widely used for the treatment of B-cell chronic lymphocytic leukemia in addition to refractory. Its use in adult organ transplantation has shown low rejection rates and minimal adverse effects. Alemtuzumab use in adult renal transplant for induction therapy followed by low dose cyclosporine demonstrated similar acute cellular rejection at 5 years with compared to triple immunosuppression therapy [139, 140]. In a prospective, randomized, single-center trial including 222 patients, immunosuppression induction with alemtuzumab or rabbit antithymocyte globulin provided similar overall survival and graft loss rates in renal and pancreas transplant patients who received the same maintenance immunosuppression, including a calcineurin inhibitor, and prophylaxis regimen. Acute rejection was significantly less with alemtuzumab and maintained at 3 years post-transplant. The incidence of fungal infections was similar between groups, and the incidence of polyoma viral nephropathy was lower in the alemtuzumab group [141].

In a study of 42 pediatric renal transplant patients at Pittsburg, induction with alemtuzumab followed by post-transplant low dose tacrolimus monotherapy resulted in a 4 year graft and patient survival of 85.4 % with a cumulative acute cellular rejection rate of 4.8 %. The authors reported no tissue invasive CMV disease or infection, no BK/polyoma viral nephropathy, and no PTLD [132].

Non-depleting Antibodies: Daclizumab and Basiliximab

There are two non-depleting antibodies currently being used in transplantation for induction. Daclizumab and basiliximab are two anti-IL-2R receptor antagonists. Because expression of IL-2 receptor (CD25) requires T-cell activation, anti-CD25 antibodies cause little depletion of T-cells. Anti-CD25 antibodies are moderately effective in reducing acute graft rejection. They are generally used in combination with calcineurin inhibitors, corticosteroids, and mycophenolate mofetil. They appear to have minimal toxic effects [142].

Basiliximab

Basiliximab (Simulect) is a chimeric (murine/human) monoclonal antibody produced by recombinant DNA technology. Basiliximab specifically binds to and blocks the actions of the interleukin-2 receptor alpha chain, on the surface of activated T lymphocytes.

Pharmacologic Considerations

Basiliximab functions as an IL-2 receptor antagonist by binding to the alpha chain of the high affinity IL-2 receptor complex and inhibits IL-2 binding. Via this mechanism, basiliximab impairs the response of the immune system to antigenic challenges. In both adults and children, there is a dose proportional increase in C-max and AUC. In adults, the volume of distribution at steady state is approximately 8.6 l. The terminal half-life in adults is a mean of 7.2 days. The half-life does not appear to be influenced by age, gender or race. In children between the ages of 2 and 11 years, the volume of distribution at steady state is approximately 5.2 l and the terminal half-life is longer at a mean of 11.5 days. The volume of distribution for basiliximab and clearance are reduced by approximately 50 % in children compared to adult patients. In adolescence, the volume of distribution and half-life are similar to adult patients [143].

The binding of basiliximab to the IL-2R is complete and consistent as long as serum concentrations exceed 0.2 micrograms per milliliter. As serum concentrations fall below this level, the IL-2R sites are no longer fully bound, and a number of activated T-cells expressing unbound IL-2R returns to pre-therapy levels within 1–2 weeks. With the recommended dosing regimen for basiliximab, the mean duration of basiliximab saturation of IL-2R is approximately 36 days. Because basiliximab is a non-depleting agent, there is no significant change to circulating lymphocyte counts or phenotypes.

Dose and Administration

Basiliximab is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation. It has also been studied and is widely used in liver and heart transplantation. The clinical and efficacy studies of basiliximab were conducted in order to provide 30–45 days of IL-2R saturation. As such, the first dose of basiliximab was administrated within 2 h prior to transplantation surgery (day 0) and the second dose administered on day 4 post-transplantation. Patients in studies utilizing this regimen experienced a significantly lower incidence of biopsy confirmed rejection episodes at both 6 and 12 months post-transplantation [144, 145]. Basiliximab is generally used as part of an immunosuppressive regimen at induction. The regimens usually include cyclosporin or tacrolimus, and corticosteroids. Some centers also utilize mycophenolate mofetil.

In adult patients, basiliximab is given in two doses of 20 mg each. The first dose is given within 2 h prior to transplantation surgery, and the second 20 mg dose is given on day 4 following transplantation. For children and adolescents, the recommended regimen is 12 mg/m^2/dose, up to a maximum of 20 mg/dose. The first dose should be given within 2 h prior to transplantation, and the second dose given on day 4 following transplantation.

Adverse Effects and Toxicity

Because basiliximab is a non-depleting antibody, the cytokine release syndrome has not been reported following basiliximab administration. Anaphylactic or anaphylactoid reactions have not been observed following basiliximab

administration. Basiliximab does not appear to be very immunogenic. The incidence of development of anti-idiotypic antibodies occurs in approximately 1/250 patients treated. There does not appear to be significant deleterious clinical effect upon the patient who develops these anti-idiotypic antibody responses. Re-administration of basiliximab following an initial course, has not been well studied in patients. As such, there is potential risk of anaphylaxis/anaphylactoid reactions following re-administration of basiliximab.

There have been no formal drug interaction studies with basiliximab. During clinical trials of basiliximab, the following medications have been administered: ATG/ALG, azathioprine, corticosteroids, CyA, mycophenolate mofetil, and OKT3. In two large safety and efficacy trials in adult patients receiving kidney transplants, basiliximab did not appear to add significant adverse events to the background profile of adverse events seen in organ transplant patients. Similarly, the overall incidence of post-transplant malignancies among patients receiving basiliximab and those receiving placebo over a 12 month follow-up, was not different. The rate of CMV infection and disease, and all other serious infections have also been similar in basiliximab and placebo treatment groups [144, 145].

Efficacy

In adult renal transplant patients, safety and efficacy randomized double-blind, placebo-controlled, multicenter trials have shown that basiliximab as part of a standard immunosuppressive regimen including CyA (Neoral®), and corticosteroids administered as described above, can reduce acute graft rejection episodes, graft loss by 15–20 % over the first 6–12 months. A clinical study comparing basiliximab with early Neoral® versus ATGAM® with delayed Neoral® in kidney transplant recipients, revealed a similar incidence of biopsy proven acute graft rejection at 6 months and a similar graft and patient survival [146]. The overall safety profile was also similar in the two groups. Based on a more convenient two-dose regimen with basiliximab, and comparable effectiveness to ATGAM, the authors concluded that basiliximab may be a more desirable induction agent. Rapid corticosteroid withdrawal or steroid-free regimens are also now becoming more widely accepted. This is in part due to clinical trials which have demonstrated that basiliximab, when given in conjunction with Neoral® and mycophenotate motetil at induction, is as effective whether also using a standard steroid treatment or a rapid steroid removal [147]. The ability to remove corticosteroids early or not use them at all appears to improve the overall adverse effect profile for the transplant recipient. Clinical efficacy studies in pediatric transplantation also demonstrate a reduction in the incidence of acute graft rejection during the first 6 months post-transplantation. Similar to adult patients, there appears to be no significant increased adverse profile, and no significant increased incidence of infections with the use of basiliximab.

Daclizumab

Daclizumab (Zenapax) is an immunosuppressive humanized IgG monoclonal antibody produced by recombinant DNA technology, which specifically binds the alpha subunit of the IL-2 receptor which is expressed on surface of activated lymphocytes. Daclizumab has now also been widely used in transplantation during the induction phase post-transplantation [148, 149].

Pharmacologic Considerations

Daclizumab functions as an IL-2 receptor antagonist by binding the Tac subunit of the IL-2 receptor complex and thus inhibits IL-2 binding. Daclizumab binding is highly specific for Tac. This is expressed on only activated, not resting lymphocytes. In clinical trials involving kidney transplant patients, 1 mg/kg intravenous dose of daclizumab every 14 days for a total of five doses demonstrated peak serum concentrations ranging from a mean of 21 μg/mL following the first dose and up to 32 μg/mL following the fifth dose. The mean trough serum concentrations were 7.6 μg/mL. Studies suggest that serum levels of 5–10 μg/mL are necessary for full saturation of the Tac subunit of the IL-2 receptor. The estimated terminal elimination half-life for daclizumab is approximately 20 days and ranges from 11 to 38 days. The mean elimination half-life of 20 days is similar to the terminal elimination half-life for human IgG (18–23 days). No dosage adjustments are required based on age, race, and gender in kidney transplant patients.

At the recommended dosing regimen, daclizumab saturates the Tac subunit of the IL-2 receptor for approximately 120 days post-transplant. The duration of clinically significant IL-2 receptor blockade is not known. Since daclizumab is a non-depleting antibody, there is no change in circulating lymphocyte counts or cell phenotype. Similarly, the cytokine release syndrome has not been observed following daclizumab administration. Similar to basiliximab, daclizumab has not been shown to have significant drug interactions with other commonly used immunosuppressive agents or antiviral agents used in transplantation.

Dose and Administration

Daclizumab is supplied in a single use vial containing 25 mg of daclizumab in 5 mL solution. The Daclizumab should be mixed with 50 mL of sodium chloride solution and administered by a peripheral or central vein over a 15 min period. Daclizumab is used during the induction phase post-transplantation as part of a regimen which includes CyA or tacrolimus, and corticosteroids. Some centers also utilize mycophenolate mofetil. Based on clinical trials, the standard course of daclizumab is five doses, with the first dose being given no more than 24 h before transplantation, and the four subsequent doses being given at an interval of every 14 days.

No dosage adjustment is necessary for patients with severe renal impairment, hepatic impairment, or age, gender or race. The recommended dose is 1 mg/kg per dose.

Adverse Effects and Toxicity

Daclizumab has a similar adverse effect and toxicity profile to basiliximab. Severe hypersensitive reactions following administration of daclizumab have been reported rarely, and therefore medications for treatment of anaphylactic reactions should be available during daclizumab infusion. Re-administration of daclizumab is also not common, and therefore the risk of anaphylaxis or anaphylactoid reactions following re-administration are not well described. Development of anti-idiotype antibodies to daclizumab have been detected in up to 8.4 % of patients treated with daclizumab. The consequence of these anti-idiotype antibodies to daclizumab have not been well characterized. Daclizumab has a low side effect profile similar to basiliximab. The randomized safety and efficacy clinical trials have not demonstrated an altered adverse effect profile when used in association with other immunosuppressive agents compared to placebo [149, 150]. Similarly, there has been no increased incidence of malignancies noted with the use of daclizumab. Specifically, daclizumab does not increase the incidence of post-transplant lymphoproliferative disorder. Overall incidence of infections including CMV infection is similar to placebo. The one exception with regard to infection is an increase in the incidence of cellulitis and wound infections in patients treated with Daclizumab compared to the placebo treated groups.

Efficacy

Clinical efficacy studies of daclizumab when given in combination with CyA and corticosteroid, or CyA, corticosteroid and azathioprine have shown a reduction in biopsy proven acute graft rejection episodes within the first 6 months following transplantation. This reduction in acute graft rejection was by 19 and 13 % respectively. When used in a double therapy regimen, there was also a significant improvement in patient survival. There was a trend in improved graft survival in both studies. When compared to placebo, daclizumab administration in combination with cyclosporin, mycophenolate and steroids, also shows a trend towards reduction in acute graft rejection at 6 months [148, 149]. Daclizumab has also been used in pediatric transplantation as part of induction therapy with good success. A lower rate of graft rejection, accompanied by an improved toxicity profile has been seen [150].

Glucocorticoids

Corticosteroids have been used in clinical transplantation since the beginning and their anti-inflammatory and immunosuppressive effects on T cell-mediated and the delayed-type tissue hypersensitivity responses have been known for decades. Only in the last 15 years has their inhibition of cytokine gene expression become clear. As such, they have a significant role in the inhibition of the costimulation of T cells by the cytokines that fully activate and commit them to proliferation and differentiation. Corticosteroids remain an essential part of the immunosuppression regimens today, but generally at lower doses than used in the past.

The mechanism by which steroids inhibit transcription of T-cell cytokines such as IL-2, IL-4, IL-5 and IFNy and IL-1 and IL-6 production in antigen-presenting cells can be summarized as follows. Corticosteroids diffuse readily into cells and bind to a cytoplasmic steroid receptor complex that is associated with a heat shock protein (HSP90). The steroid-receptor complex is chaperoned to the nucleus, where prior to entry the HSP90 protein dissociates. In the nucleus the complex binds to other proteins (HSP56) that carry it to the primary site of action. These proteins dissociate and the DNA-binding domain of the receptor is uncovered and binds to its DNA site referred to as glucocorticoid response elements (GRE). GRE sequences exist in the promoter regions of several cytokine genes. Corticosteroids also inhibit the translation of mRNA for TNFα and IL-1 and decrease the stability of that mRNA. In addition, corticosteroids may also have an inhibitory effect on the expression of adhesion molecule on both leukocytes and endothelial cells. There is evidence that corticosteroids play a role in blocking important steps involved in the effector mechanisms. Eicosanoids are chemotactic agents that attract leukocytes to sites of inflammation and steroids inhibit the production of eicosanoids by macrophages.

The pharmacology of glucocorticoids is well described elsewhere and will not be discussed here. The glucocorticoid potency of the various available steroids is different. Methylprednisolone has a potency five times, prednisolone four times, prednisone four times, and dexamethasone 25–30 times the potency of hydrocortisone. The corticosteroids with the least mineralocorticoid effects are preferable. The specifics of each regimen will differ from center to center. In general it is believed that anti-inflammatory and immunosuppressive doses for methylprednisolone are in the 0.15–1 mg/kg/day range or 5–25 mg/m^2/day. During the induction phase many protocols use doses as high as 10 mg/kg/day, and the dose is decreased slowly to maintenance doses of 0.15–0.25 mg/kg/day of prednisone. Corticosteroids can be given once a day; however, split doses given twice daily must be considered in patients exhibiting problems with hypertension, hyperglycemia, fluid retention, excessive weight gain, aggressive or unusual behavior (*steroid psychosis*), or interference with metabolism of other drugs such as CyA or tacrolimus resulting in elevated blood concentrations beyond the therapeutic range. The short-term and long-term adverse effects of glucocorticoids, well described elsewhere, are beyond the scope of this chapter.

Rapid tapering of corticosteroid doses has become the standard practice in de novo solid organ transplantation of all organs excluding small bowel and lung transplants. Several investigators are also using steroid free protocols. Long term outcomes with these protocols is not yet available, however the addition of anti-IL2R monoclonal antibodies at induction, the improved understanding of the use and TDM of CyA and tacrolimus, and the use of mycophenolate mofetil are key in allowing early steroid withdrawal or eliminating steroid use altogether. This development should greatly improve the overall side effect profile for pediatric transplant recipients and improve their post-transplant quality of life [34, 62, 151–154].

Conclusion

Many advances in clinical transplantation and in the development of specific immunosuppressive agents have occurred over the past three decades, however, acute and chronic allograft rejection remains one of the leading causes of graft failure and loss. There is a clear link between the discovery of new immunosuppressive agents and our understanding of the cellular and molecular biology of the immune system and its response to foreign antigens. In clinical transplantation, immunosuppressive agents are used to achieve a maintenance level of immunosuppression with the goal of preventing graft rejection and yet avoiding side effects and providing an excellent quality of life. As such we must learn and monitor all immunosuppressive agents for their immunosuppressive effect (therapeutic effects), their immuno-deficient effect (over immune-suppression), and their non-immune toxic effects.

It is the hope of all transplant clinicians that the future will hold the key to finding the appropriate balance between these three effects on our patients. At present, strategies to limit the doses and TDM of the calcineurin inhibitors, usage of adjunctive therapies such as the antiproliferative agents, use of inhibitors of the secondary activation signals, and limiting or withholding corticosteroids may be the best tools available. In the future, inhibiting the early steps of allorecognition and finding strategies to induce tolerance will be the goal.

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Heart Transplantation

27

Clifford Chin and John Lynn Jefferies

Abstract

Heart transplantation has long been an acceptable form of pediatric therapy for end-stage heart failure secondary to genetic or acquired cardiomyopathy. Other indications include heart failure after palliation of congenital heart disease or for congenital heart disease not amenable to standard surgical approaches. Over the decades, survival outcome after pediatric heart transplantation has improved. Optimal post-transplant outcome can be attributed to all phases of care including the identification, evaluation, and care of the pre-transplant candidate, intra-operative and immediate post-operative approaches, and long-term management.

Keywords

Heart failure • Heart transplantation • Mechanical circulatory support • Immunosuppression • Antibodies • Rejection • Coronary allograft vasculopathy

Introduction

The race to perform the first human heart transplant legitimately began during the 1960s with the pioneering work in the laboratory by Drs. Shumway and Lower, who led the field in developing a better understanding of surgical technique and post-operative immunosuppression. The first human heart transplant operation in the United States was done by Dr Adrian Kantrowitz in an 18-day-old male infant, which occurred just 3 days after the first historic event was performed by Dr. Christiaan Barnard in South Africa [1, 2]. Survival in these early days, however, was quite poor with the 1 year survival rate approximating only 20 % and death attributed to a poor understanding of immunosuppression. As a result, only a handful of cardiac transplant operations were performed in the 1970s. Under the direction of Dr. Shumway, survival outcomes improved through the treatment of histologic confirmed rejection through innovations like the creation of a new biopsy forcep [3] and the histologic grading system developed by Margaret Billingham [4]. One-year survival in the late 1970s to early 1980s rose to 63 %. Today, excellent outcomes after pediatric cardiac transplantation have been achieved.

The International Society for Heart and Lung Transplantation (ISHLT) registry was created in the early 1980s, tracking outcomes for pediatric heart recipients (< 18 years of age at the time of transplant). Over the ensuing decades, the annual number of children undergoing cardiac transplantation within the ISHLT registry appears to have grown from less than 50/year to over 500/year (Fig. 27.1) [5]. According to the 2011 Annual Data Report from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR), the volume has risen with greater than 1,090 pediatric hearts

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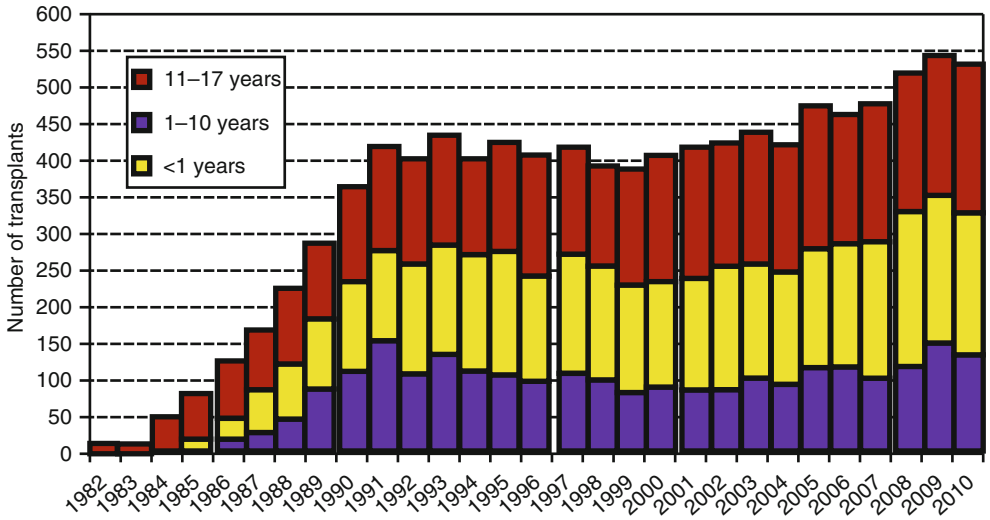

Fig. 27.1 Annual volume and distribution of pediatric heart transplant recipients reported to the transplant registry of the ISHLT (Reprinted from Kirk et al. [5]. With permission from Elsevier)

implanted in the years between 2009 and 2011 [6]. Statistically significant improvements in outcomes reported for children in the ISHLT registry have also been observed with current 1, 5, and 10 year survival roughly at 90, 75, and 65 % respectively (Fig. 27.2) [5].

The approach to the critically ill child in the intensive care unit (ICU) requires intensive management considerations, as the state of the candidate heading into transplantation often greatly influences post-operative outcomes. Statistically significant candidate risk factors for early mortality post-transplantation include a pre-transplant diagnosis of congenital heart disease, redo heart transplant, renal function (i.e., creatinine), dialysis or ventilator dependence, human leukocyte antigen (HLA) sensitization, and recipient age (i.e., infants) [7]. The purpose of this chapter is to highlight the approach to the critically ill child who may be in need of transplantation to ensure most optimal outcomes.

Identification and Evaluation of the Pre-transplant Candidate

The goals of transplantation are both to prolong life and to improve the quality of life. The selection of appropriate patients for transplantation to achieve these goals is therefore critical. It is important to have set criteria or guidelines to ensure non-discriminatory selection with optimal outcomes. Critically ill children are often presented to the heart failure/heart transplant team for consideration of transplant listing. Most, but not all patients who are in need of transplantation are appropriate for transplant listing. Many factors to consider include medical, surgical, and psychosocial issues. The evaluation process oftentimes is lengthy to ensure complete knowledge of the risks and benefits of transplantation and to identify alternatives to transplantation. Knowledge of the aforementioned factors allows for complete informed consent for the potential transplant candidate and family.

Pre-transplant Evaluation

The medical evaluation of the potential transplant candidate should first identify whether the child is in need of transplantation. A subset of patients may have medical and/or surgical considerations that would either negate or delay the need for transplant listing. Over the past decade, advances in heart failure therapies have improved ventricular performance and overall clinical status. Beta blockade, for example, has been associated with improvements in systolic performance by echocardiography as well as improvement in functional status, potentially delaying the need for transplant listing [8–15]. Other aspects of the medical evaluation include a complete review of medical and surgical histories, including data from ancillary tests. Echocardiography gives insight as to ventricular performance, potentially identifying surgical options or, in cases of significant ventricular dysfunction, the need for additional medical therapies (e.g. anticoagulation). Cardiac catheterization data is often required to determine hemodynamics, particularly indexed pulmonary vascular resistance (PVRi). Most pediatric centers accept a PVRi < 4–6 Wood units. Acceptance of PVRi, however, is center specific as post-transplant death secondary to right heart failure can be influenced by pre-transplant pulmonary reactivity. Historically, a PVRi > 6 Wood units was considered an absolute contraindication to transplantation [16]. Subsequently, some have demonstrated use of acute or chronic pulmonary vasodilator therapy or afterload reduction therapy with repeat catheterization to rehabilitate the candidate's PVR to an acceptable level [17–21]. Other assessments may include the use of CT angiography or cardiac MRI to delineate cardiac

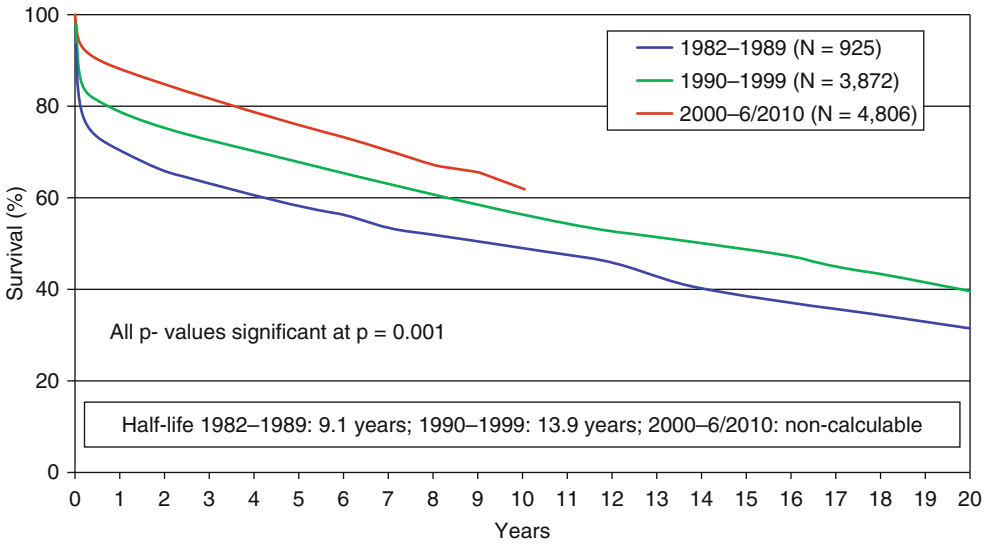

Fig. 27.2 Kaplan-Meier survival by transplant era (Reprinted from Kirk et al. [5]. With permission from Elsevier)

anatomy and positioning relative to the chest, pulmonary and systemic venous patency and anatomy. Complete understanding of abnormal systemic venous return facilitates advanced planning for donor procurement of extended venous harvest and complicated surgical anastomoses.

The medical evaluation should also include an assessment of biomarkers for end organ insufficiency including renal and hepatic dysfunction, as immunosuppressive therapies post-transplant can lead to functional impairments. Renal insufficiency pre-transplant is a known risk factor for pediatric heart transplant mortality [7]. Hepatic dysfunction and cirrhosis likewise are risks for morbidity and mortality [22].

Indications and Contraindications

Indications for transplant consideration include failed palliation for congenital heart disease, congenital heart disease not amenable to surgical palliation, end-stage cardiomyopathy, non-resectable cardiac tumors, and post-transplant vasculopathy. Medical contraindications to transplantation include active malignancy, sepsis, medical non-compliance and other psychosocial issues, active substance abuse, elevated pulmonary vascular resistance, and obesity. A large, multicenter adult study published by The Cardiac Transplant Research Database Group demonstrated that pre-transplant obesity is related to post-transplant morbidity (i.e. infection) and mortality [23]. Contrary, a large, multicenter pediatric study using the ISHLT registry did not find obesity to be a risk factor for adverse post-transplant outcomes [24]. Additional contraindications to transplant listing include a patient who is either too ill to undergo transplantation with multisystem organ dysfunction and those who are too well to undergo transplantation.

The importance of selecting out candidates from transplant listing stems from a donor shortage issue. Reducing the number of patients vying for the same organ on the waitlist could positively impact the survival for those waiting for transplantation. According to the OPTN/SRTR 2007 Annual Report, death while waiting for cardiac transplantation recently has ranged from 7 to 28 % for the years 2003–2007 [25]. Among pediatric patients, however, death while waiting for transplantation is much higher. For those between 0 and 5 years of age, death while waiting for cardiac transplantation ranged from 7 to 28 % between the years 2003 and 2006. A major factor for death while awaiting transplantation was a limited donor pool. Infants are at particular risk due to limitations in donor availability with single and multi-institutional reports of pre-transplant mortality ranging from 25 to 33 % [26–29]. Contemporary waiting list mortality among 3,098 children in the United States listed for heart transplantation between 1999 and 2006 was 17 % [30]. Status 1A candidates, those considered the sickest, had a mortality rate of 20 % by 6 months on the waiting list. Within the status 1A group, those who required ECMO or mechanical ventilation were at highest risk for death while waiting for transplantation [30]. Finite longevity of a cardiac graft is the primary reason why those who are too well are deferred for transplantation. Given the current 1 and 5 year post-transplant survival outcomes, those who have equal or better survival with medical or surgical therapies would benefit from avoiding or delaying transplantation.

Psychosocial Factors

Psychosocial risks factors are of paramount importance as heart transplant recipients are dependent upon multiple medications and medical interventions to ensure graft and patient

survival. Some centers have utilized social workers and clinical psychologists to help in the evaluation process. Aspects to consider include social, personal, housing, vocational, financial, and environmental supports. The patient and family need to understand the risks and benefits of transplantation, especially the need for chronic medication therapy and their potential side effects. The ability to adhere to a pre-transplant therapeutic regimen is often telling of how a patient and/or caretaker will react post-transplant. The mental health history, including substance and alcohol use/abuse, may influence the impact of transplant success since high risk behaviors could translate into risk taking behaviors (medication non-compliance) post-transplant. Reluctance or refusal to participate in a mental health regimen likewise gives insight into whether the patient and/or caregiver will comply with the rigors of post-transplant care.

Management of the Pre-transplant Candidate

The appropriate management of the pre-transplant patient can have a major impact on intra-operative and post-operative outcome. The goal should be to provide the best candidate possible at the time of transplantation. This involves a global assessment of end-organ function, nutritional status, optimization of cardiac and volume status, and careful surveillance of factors that may preclude isolated cardiac transplant, such as active infection or significant, irreversible end-organ damage such as a cerebrovascular accident (CVA). Ongoing management of advanced heart failure may include various medical and interventional strategies, including cardiac pacing or placement of an implantable cardioverter defibrillator (ICD), or mechanical support such as ventricular assist devices or extracorporeal membrane oxygenation (ECMO).

The use of oral therapies to reduce afterload and promote ventricular remodeling are usually indicated based on current guidelines [31]. These recommendations are based on largely adult data given the relatively paucity of pediatric investigation. However, most centers apply these recommendations to their pediatric and adolescent patients. Although discussed in other chapters in this textbook, the suggested approach to chronic therapy should include the use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) if patients are ACEi intolerant. Addition of beta-blocker therapy in the form of metoprolol or carvedilol is also recommended for afterload reduction, preservation of myocardial function, and favorable ventricular remodeling. Judicious use of loop diuretics is advocated for amelioration of congestive symptoms, but should be avoided chronically given the possibilities of worsening renal function. Potassium sparing diuretics such as spironolactone may be considered to improve cardiac related symptoms and limit and/or reverse cardiac fibrosis. These therapies may be instituted and titrated in either the inpatient or outpatient setting with ongoing non-invasive surveillance to assess for improvement or worsening of clinical status. However, many patients will progress either with chronic worsening of myocardial function and/or signs and symptoms of chronic heart failure.

Patients may present with evidence of acute decompensated heart failure (ADHF) requiring admission and escalation of care. Clinical assessment with careful history and physical examination of patients in ADHF can be invaluable in choosing optimal inpatient care. Bedside examination should be targeted at assessing the patient's volume status and perfusion. For those patients with evidence of volume overload with preserved tissue perfusion, prompt intravenous therapy should be initiated with a goal of symptom relief and euvolemia. If this cannot be accomplished with diuretics, intravenous afterload reduction should be considered. Nitroglycerin, nitroprusside, or nesiritide are possible options. Many centers, including our own have extensive experience with nesiritide and have found it to be well tolerated in children. In the setting of poor perfusion and low cardiac output, consideration of inotropes may be appropriate. Dopamine, dobutamine, milrinone, or epinephrine are all considerations, but therapy should be tailored to the clinical situation. The use of beta-adrenergic therapy likely should be avoided in tachycardic patients. Similarly, use of milrinone or dobutamine, may be inappropriate in patients that are hypotensive. There is increasing recognition in adult and pediatric heart failure management that inotropes are harmful to the myocardium and should be used sparingly and for as limited a duration as possible.

It is our practice that when patients have progressed to the need for intravenous therapy in the form of vasoactives and/or inotropes, care should be delivered in the controlled environment of the ICU. During this time, oral therapies may be discontinued. Beta blockers should be held in the setting of poor perfusion given their negative inotropic effects. Patients may achieve compensation and be restarted on their oral therapies. For those patients with evidence of severely depressed LV systolic function (LVEF <35 %), consideration may be given to placement of an implantable cardioverter-defibrillator (ICD). Experience in children is limited but this may be a life-saving therapy. Consultation with Electrophysiology may be appropriate. For adult patients with an LVEF <35 % and evidence of a left bundle branch block (LBBB) on ECG, cardiac resynchronization therapy (CRT) accomplished through biventricular pacing has been shown to reduce mortality, improve symptoms, and favorably impact systolic function [32–34]. However, appropriate use in pediatrics remains poorly defined. Our practice has employed CRT in selective cases with intermediate results. Arrhythmia management may also be an indication for admission to the ICU, even in the setting of preserved tissue perfusion as many of the commonly used agents such as amiodarone can have pro-arrhythmic effects and depress myocardial function.

End-organ surveillance is a critical component to the management of advanced heart failure. Assessment of hematologic markers, neurologic compromise via head imaging, hepatic congestion or compromise as assessed by serologic study, skeletal muscle dysfunction as assessed by functional capacity, and decrease in pulmonary function can all be invaluable indicators of heart failure compensation or conversely, signals that require additional support as outlined above. One of the most important needs for regular surveillance is assessment of renal function. Impaired kidney function has been repeatedly associated with poor outcomes in adults with heart failure. There is a complex interaction seen in adults between the heart and the kidneys which has been termed the cardiorenal syndrome (CRS) [35]. CRS also exists in pediatric patients and may play a significant role in ICU morbidity and mortality [36]. In children admitted with decompensated heart failure, worsening renal function was found to be predictive of need for mechanical circulatory support, transplant, or death [37]. As patients undergoing cardiac transplant will be maintained on chronic nephrotoxic medications, preserving kidney function is of major clinical importance.

Increasingly, patients with congenital heart disease are considered for possible cardiac transplantation. The pre-transplant management of these patients can be found elsewhere in this textbook. Many of these patients may have ductal-dependent lesions and can be listed during infancy. Often these types of patients are critically ill and awaiting transplantation in the ICU. Careful management by a multidisciplinary team is paramount to success given the increased complexity secondary to need for intervention or surgical palliations, end-organ dysfunction, ventilator management, and consideration of genetic or syndromic causes of disease as this may affect long-term outcome [38].

Some patients may continue to deterioration of clinical status requiring more advanced therapy in the form of mechanical circulatory support (MCS). This assessment may be made on multiple clinical parameters and consideration of the risk to benefit ratio for each patient. A more complete discussion of MCS strategies for management of end-stage heart failure can be found elsewhere [39]. In brief, the development of a plan for MCS should be done for all patients with heart failure admitted to the ICU as patients may acutely decompensate requiring support. Many centers would pursue ECMO as a temporary support strategy. However, we promote a different strategy that utilizes temporary devices which offer clinicians an opportunity to either bridge to recovery, bridge to a more durable form of MCS, or bridge to transplant if a graft becomes available. The increasing availability of temporary and permanent devices has greatly broadened the armamentarium for MCS [40]. The recent publication of results on the Berlin EXCOR device in pediatrics has led to the FDA approval of this device (Fig. 27.3). Ongoing VAD development for children through the Pumps for Kids, Infants, and Neonates (PumpKIN) trial should open the door for an even greater number of devices available to infants and children. For larger patients, use of existing technologies for left-sided, right-sided, or biventricular support are increasingly available in pediatric institutions [41]. Our center is actively using total artificial heart (TAH) implantation as a bridge to cardiac transplant (Fig. 27.4).

Fig. 27.3 Ten milliliter EXCOR pump (Courtesy of Berlin Heart, Inc)

Fig. 27.4 Syncardia total artificial heart (Courtesy of SynCardia.com)

Care must be given to assessment of the development of panel-reactive antibodies during the pre-transplant period. PRA testing is widely available and is performed in all

Table 27.1 Induction agents

Drug	Class	Action	Side effects
Muromonab CD3 (OKT3)	Monoclonal antilymphocyte antibody	Ablative	Anaphylaxis, cytokine release syndrome
Rabbit antithymocyte globulin (Thymoglobulin)	Polyclonal antilymphocyte antibody	Ablative	Anaphylaxis, cytokine release syndrome
Equine ATG (ATGAM)	Polyclonal antilymphocyte antibody	Ablative	Anaphylaxis, cytokine release syndrome
Basiliximab and daclizumab	Monoclonal anti-cytokine receptor antibody	Blocks interleukin-2 binding site	Hypersensitivity

transplant centers in North America. Common sensitizing agents may include blood product transfusions, homograft material such as that used in the repair of congenital heart lesions, and the use of MCS. PRA testing is an opportunity in the pre-operative period to identify anti-HLA antibodies. These antibodies may increase the risk of post-transplant antibody mediated rejection (AMR) [42]. It has been reported that a PRA >10 % is associated with increased rejection episodes and reduced survival following transplant [43]. There are strategies to mitigate elevation of the PRA in individual patients. This process, known as "desensitization", may involve many different treatment options such as plasmapheresis, intravenous immunoglobulin (IVIG), cyclophosphamide, and bortezomib [44–48]. These therapies may be used alone or in combination with varying degrees of success. However, ongoing surveillance must be performed during the pre-transplantation period and efforts should be to limit exposures that may adversely affect PRA measurements.

General Considerations

Immunosuppression

Induction

Immunosuppressive therapy typically begins either immediately pre-operatively or intraoperatively depending upon the clinical scenario and the institution. Opinions regarding the use of induction agents, use of steroids, and type of calcineurin inhibitor are prevalent in the literature. Induction therapy (Table 27.1) can be used in the perioperative period to reduce the likelihood of early post-operative allograft rejection and delay the use of calcineurin inhibition, a class of immunosuppressive drugs with nephrotoxic side effects. It should be noted, however, that induction therapy has not had a significant effect on reducing rejection episodes between time of discharge and 1-year follow up [49]. Between 2001 and 2010, there has been an increasing trend towards the use of induction therapy in children [49]. Induction was used in more than 70 % of patients with 66 % receiving polyclonal anti-lymphocyte antibody and 33 % receiving an interleukin-2 receptor blocker [7]. Although survival is not influenced by use of induction therapy, there are no increased risks for cytomegalovirus (CMV) or post-transplant lymphoproliferative disease [50].

The monoclonal and polyclonal antibodies are ablative, substantially depleting circulating lymphocytes [51]. Use of these agents significantly decreases the incidence of early cardiac allograft rejection [52–55]. Potential factors that may increase donor antigen expression and thus yield early rejection include donor brain death, ischemia/reperfusion injury, and surgical trauma [56]. Not all ablative therapies are considered equal, however. A study performed by the Pediatric Heart Transplant Study (PHTS) demonstrated that the polyclonal antibodies may be superior to OKT3 to reduce rejection frequency with an improved survival benefit [52]. Contemporary use of ablative induction therapy has all but eliminated the use of OKT3. The pediatric registry report of the ISHLT reported a less than 5 % use of OKT3 between January 2001 and June 2005 [57].

The monoclonal and polyclonal antilymphocyte antibodies all share significant morbid side effects. These classes of induction agents are prepared from non-human origins (OKT3 – mouse, Thymoglobulin – rabbit, ATGAM – horse). Anaphylaxis may result from the reactivity against the xenoantigens. The cytokine release syndrome, more common with use of OKT3, [58] is a phenomenon where cytokines are released by activated T cells before the cell is destroyed. This reaction may be indistinguishable from type I hypersensitivity [59] with symptoms including fever, nausea, chills, hemodynamic instability, headache, rash, and dyspnea. Pretreatment with acetaminophen, histamine blockers, and steroids may be preventative but when significant, temporarily halting the infusion, treating with histamine blockers, then restarting the infusion at a slower rate often mitigates the symptoms [60].

The interleukin-2 receptor antagonists are monoclonal antibodies that selectively block IL-2 receptors on activated T helper cells preventing clonal expansion. These monoclonal antibodies are genetically engineered, replacing large segments of the murine component with human amino acid sequences. The result has yielded products with decreased antigenicity and thus significant reduction in allergic side effects seen with other induction agents. Chin and coworkers compared OKT3 and daclizumab induction in 80 pediatric and adult heart transplant recipients, demonstrating

efficacious protection against morbidity and mortality between the agents [53]. Daclizumab, however, is no longer available for commercial use, removed from the world market by 2010 due to diminishing marketing demands and not due to safety concerns. Gundy and colleagues reported on the efficacy of basiliximab in a pediatric heart transplant cohort. This study suggested that the rate of acute rejection was significantly lower if the first dose was given pre-operatively before cardiac implant [61].

Alemtuzumab (Campath) is a rarely used induction agent among adult heart transplant centers [45, 62] with limited data regarding use among pediatric populations. Das and coworkers published a case report demonstrating successful use of alemtuzumab on a high risk teenage heart transplant recipient [63].

Maintenance

Maintenance immunosuppression in the post-operative period typically consists of dual or triple therapy with a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite agent (azathioprine or mycophenolate mofetil), and glucorticoid steroids. Use of proliferation signal inhibitors (mammalian target of rapamycin or mTor inhibitors) in preference of an antimetabolite agent has been limited due to early post-transplant drug related morbidities, specifically delayed sternal wound healing reported in adult heart transplant recipients [64, 65].

As stated previously, one goal of induction therapy is delayed initiation of calcineurin inhibitors due to renal toxicity. Patients in the immediate post-transplant period are at risk for renal insufficiency that can be exacerbated by these nephrotoxic immunosuppressive agents. Calcinurin inhibition, therefore, typically starts after post-operative day 1–2 once the risk subsides and renal function normalizes. Cyclosporine (CSA) was first introduced for cardiac transplant immunotherapy in the early 1980s, dramatically improving short term survival. Since then, calcinurin inhibitors have been the mainstay of chronic therapy. Tacrolimus (TAC) was introduced in 1995, initially for use in liver transplantation. Since then, pediatric cardiac transplant programs have moved toward tacrolimus based immunosuppression. The Registry of the International Society for Heart and Lung Transplantation has been producing an annual report since the 1990s. According to a recent pediatric report, primary immunosuppression at 1-year post-transplant consisted of CSA (33 %) or TAC (66 %) [49]. Both agents block activation of calcineurin, inhibiting dephosphorylation of nucleated factor of activated T cells (NF-AT) and thereby hindering production of interleukin-2 (IL-2). IL-2 is a powerful stimulant for clonal expansion of activated T cells. Debate among individual pediatric heart transplant centers continues regarding whether one agent is superior over the other although most publications cite superior reduction in acute cellular rejection among TAC treated patients [66–68]. Despite a lower incidence of acute rejection, however, studies have not demonstrated a superior survival benefit between the CSA and TAC treated patients. Both agents have unfavorable morbid side effects including hypertension, hyperlipidemia, renal insufficiency, gastrointestinal and hepatic. Side effects experienced primarily among CSA based patients include hirsuitism and gingival hyperplasia whereas those treated with TAC are at higher risk for insulin-dependent diabetes [69] and post-transplant lymphoproliferative disorder [70].

A second class of immunosuppressants are referred to as antimetabolites or antiproliferative agents. These drugs target the cell cycle, interfering with the synthesis of nucleic acids, and thus interfere with proliferation of T and B cells. Azathioprine (AZA), once commonly used, has generally been replaced by mycophenolate mofetil (MMF) since its introduction in the mid-1990s. Adult studies have demonstrated a rejection-prevention and survival benefit of MMF over AZA [71, 72]. Gastrointestinal side effects may limit the use of MMF although dose reduction often results in symptom reduction. Bone marrow suppression tends to be less common among those treated with MMF versus AZA. An alternative to the antimetabolites now includes proliferation signal inhibitors (mTOR inhibitors; Sirolimus and Everolimus). These agents bind to the FK binding protein but, unlike tacrolimus, do not work through the calcineurin pathway. The target of rapamycin (TOR) is a kinase that regulates cell proliferation in response to IL-2. Sirolimus and Everolimus inhibits TOR and thus inhibits T and B cell proliferation in response to IL-2. Many centers avoid use of the mTOR inhibitors in the immediate post-transplant period primarily due to issues related to sternal wound healing [65].

Glucocorticoids have been used for maintenance immunosuppression since the infancy of cardiac transplantation. These agents are commonly used as part of induction therapy alone or in combination with the other induction agents. Side-effects tend to limit use long term and include hypertension, cosmetic (cushingoid features, obesity, cutaneous), myopathy, and endocrine (hyperlipidemia, salt retention, diabetes mellitus, osteopenia, and growth retardation). Common strategies to reduce steroid induced morbidities include steroid-sparing protocols, steroid-avoidance protocols, and rapidly tapering protocols. Despite the morbid effects, high dose methylprednisolone has been the mainstay of therapy for suspected or confirmed high-grade rejection.

Immediate Post-operative Complications

Primary Graft Failure

Primary graft failure is the most common cause of death in the early post-operative period [73]. It manifests as severe allograft dysfunction of unknown etiology, necessitating use of inotropic agents. Infants, in particular, are at greatest risk for mortality secondary to acute post-operative graft failure

[74]. The authors theorized a greater risk in this population due to donor factors, perioperative preservation, reperfusion injury, and elevated pulmonary vascular resistance in the recipient. Regardless of cause, post-operative management of all transplant recipients requires close monitoring of hemodynamics for primary graft failure. It is in our experience to continue inotropic agents (milrinone ± epinephrine) and consider inhaled nitric oxide for the first few days post-transplant primarily to support the right ventricle.

Right Heart Failure

Recipients with pre-operatively elevated pulmonary vascular resistance (PVR) are of particular concern for early right heart failure leading to death. The right ventricle is a thin-walled pumping chamber that can adapt to high afterload but not under acute conditions. Management of right heart failure due to elevated PVR requires the clinician to identify patients before transplantation. Echocardiography can be used to estimate right ventricular pressure but cardiac catheterization for confirmation should be considered, especially for those with the history of restrictive cardiomyopathy. Individual institutions have their own threshold for PVR that are absolute contraindications for cardiac transplantation but typically range from 6 to 8 Wood Units (indexed to body surface area). Heightened concern for PVR issues, however, remains necessary even for those whom did not have elevated resistance in the pre-transplant period. Inter-operative factors that can cause early right heart failure in the immediate post-transplant period include bleeding and blood replacement, ischemia/reperfusion injury, cardiopulmonary bypass, pulmonary infections, and an undersized donor heart. Strategies to overcome PVR issues include oversizing the donor allograft or use of domino heart transplants from recipients undergoing combined heart-lung transplantation for pulmonary diseases. Therapy for elevated PVR in the post-operative period includes sedation, close attention to acid-base status, oxygen, inotropic support and use of inhaled pulmonary vasodilators with transition to oral sildenafil. In extreme cases, institution of mechanical right heart support may be necessary.

Late Postoperative Complications

Rejection

Monitoring the transplant recipient for acute cellular allograft rejection is a key to short- and long-term survival. The risk of rejection in children is greatest in the first 3 months post-transplant [75]. Although attempts to noninvasively diagnose rejection have been made [76–79], cardiac biopsy remains the "gold standard." Repeated cardiac catheterization and biopsy, however, is not without risk including loss of vascular access, perforation, and damage to the tricuspid valve. The risk is greatest among the smallest of transplant recipients, especially infants. Many pediatric programs have reduced the frequency and number of biopsy procedures in infants and small children, using history (feeding intolerance, fever, irritability, and lethargy), physical examination (presence of a new murmur or a gallop rhythm), and noninvasive tests (primarily echocardiography) to guide the clinician. Recipient age appears to be a risk factor for acute cellular rejection with infants at lowest risk and adolescents at greatest risk [80]. Treatment of acute cellular rejection depends upon the grade of rejection but can be influence by the presence or absence of hemodynamic compromise. Typically high-dose steroids are the first line treatment of suspected or biopsy proven rejection. High-grade rejection often is treated with a course of ATG.

Diagnosis and treatment of acute cellular rejection had taken center stage for many decades. Recently, however, rejection mediated through activation of complement (antibody mediated rejection, AMR) has gained wider appreciation. Antibody formation against human leukocyte antigens (HLA) can develop after certain exposures. Children with congenital heart disease may be at particular risk, especially those who have undergone surgery using human homograft tissue, received a ventricular assist device, or have been exposed to multiple blood products [81–88]. Strategies to prevent against AMR in heart and other solid organ transplant recipients include pre-, intra-, and post-operative transplant desensitization with IVIG, plasmapheresis, immunoadsorption, and immunosuppression [46, 89–105]. A 2010 consensus conference defined AMR as a pathologic entity consisting of endothelial cell swelling, accumulation of intravascular macrophages, interstitial edema and hemorrhage, and presence of neutrophils in and around capillaries [106, 107]. Therapy of symptomatic AMR typically includes treatments used for cellular rejection with the addition of plasmapheresis, IVIG, or both [108–110]. Rituximab, an anti-CD20 monoclonal antibody, has been used to treat AMR [89, 111, 112]. We have utilized a strategy that begins in the pre-transplant waiting period. Identification of antibodies that can bind complement and activate the complement cascade is a key factor to our protocols [113]. One can utilize assays to detect complement fixing antibodies and list the corresponding antigen(s) as avoids with the United Network for Organ Sharing (UNOS). For those who are highly sensitized against HLA antigens, pre-transplant desensitization with IVIG can be successful. Successful reduction of PRA among highly sensitized pediatric heart transplant candidates with IVIG monotherapy, personal communication). Other pediatric heart transplant centers have reported successful transplantation of highly sensitized candidates combining plasmapheresis and thymoglobulin induction [44, 114].

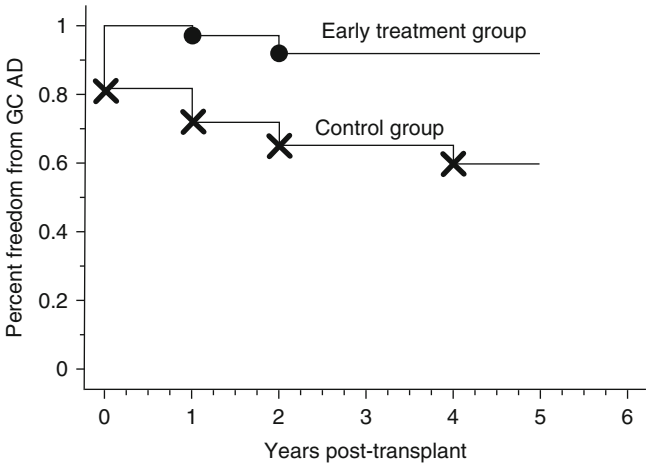

Fig. 27.5 Freedom from CAV based on atorvastatin therapy. The early treatment group includes patients that were started on atorvastatin before the ninth-week post-transplant. The control group comprised of patients who did not receive atorvastatin before the ninth-week post-transplant and include those who never received the drug in their transplant history (Reprinted from Chin et al. [115]. With permission from John Wiley and Sons, Inc)

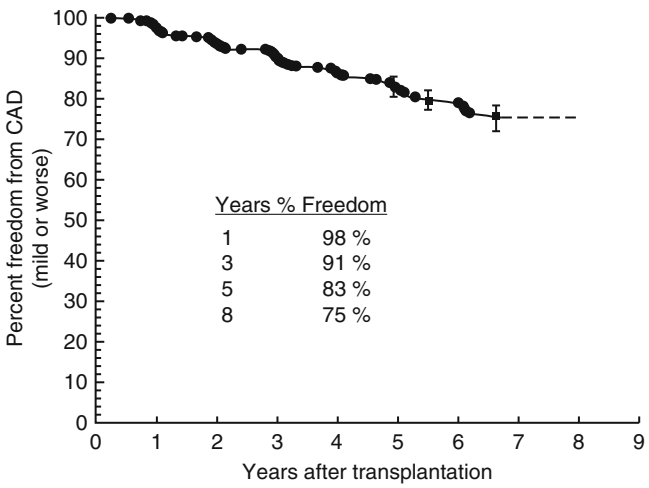

Fig. 27.6 Actuarial freedom from angiographic CAV (Reprinted from Pahl et al. [116]. With permission from Elsevier)

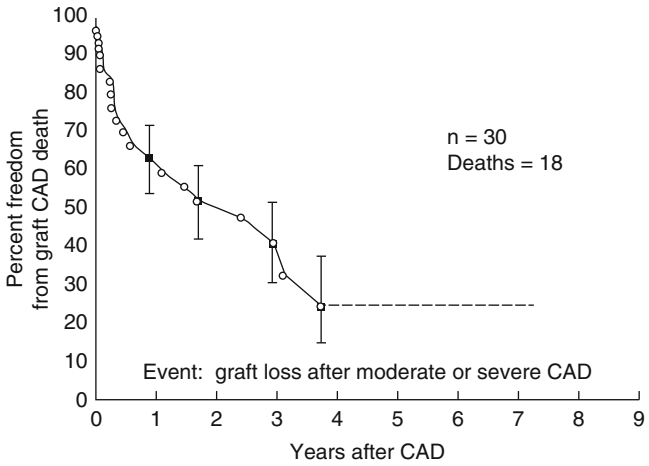

Fig. 27.7 Actuarial survival after diagnosis of moderate to severe CAV (Reprinted from Pahl et al. [116]. With permission from Elsevier)

Coronary Artery Vasculopathy

Coronary artery vasculopathy (CAV) is a major cause of morbidity and mortality primarily beyond the initial post-transplant year. There is evidence, however, that events and pertubations in the peri-operative and early post-transplant period may play crucial roles in the eventual development of CAV. Chin and co-workers reported on 65 pediatric subjects; 33 received atorvastatin early after transplant and 32 did not receive the drug at all or within the study time entry criteria (within the first 2 months post-transplant) [115]. Fourteen patients had angiographic evident CAV, two whom received atorvastatin early after transplant and 12 whom did not. Greater freedom from CAV was seen in the early atorvastatin treated group compared to the control group (Fig. 27.5, ($p < 0.005$). Therefore, initiation of statin therapy early after transplantation may be protective against future development of CAV. Pahl and PHTS co-workers reported that the incidence of any angiographic CAV was <20 % by 5 years post-transplantation (Fig. 27.6). Outcome after diagnosis of moderate-to-severe CAV by angiography was poor with a 50 % likelihood of death by 2 years post-CAV diagnosis (Fig. 27.7). Incidence of high grade disease at 5 years post-transplant was low (5 %) and statistically lower than that reported among adult recipients [116].

Diagnosis of CAV by angiography has limitations, especially given that transplant vasculopathy often is diffuse rather than focal. Intravascular ultrasound (IVUS; Fig. 27.8), however, is a more sensitive modality to assess for intimal proliferation, the hallmark of CAV. The first IVUS study among pediatric patients ≥5 years post-transplant reported a 74 % prevalence of disease [117]. There is little pediatric data associating IVUS with post-transplant outcomes but we do gain insight into the relationship from our adult colleagues. Kobashigawa and co-workers validated in a large multicenter study that IVUS is a reliable surrogate marker for poor outcomes. Specifically they found that progression of the maximal intimal thickness ≥0.5 mm in the first year was associated with a greater mortality risk, subsequent non-fatal major adverse cardiac events, and greater risk of angiographic disease within 5 years after transplantation [118]. We have published additional data regarding possible risk factors for graft loss and coronary artery vasculopathy. Based on previous data, it is widely recognized that many patients, children and adults, suffering from dilated cardiomyopathy may harbor evidence of viral presence in their myocardium. This viral infection of the myocardium can be diagnosed using EMB as discussed above with assessment for viral

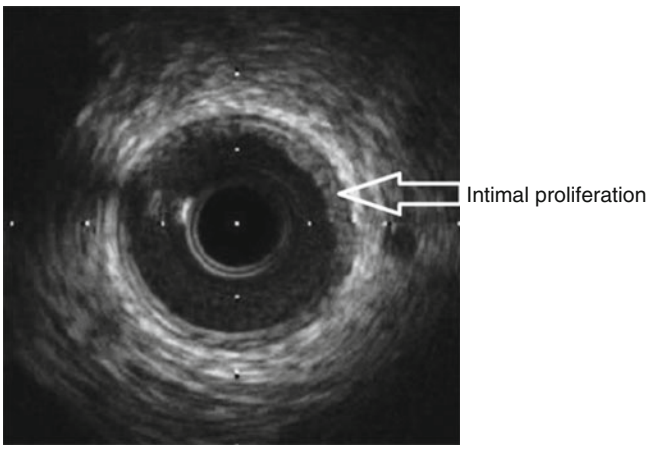

Fig. 27.8 Intravascular ultrasound (IVUS) image with intimal proliferation (Courtesy of Clifford Chin, M.D)

PCR. The presence of viral infection in a donor heart following transplantation was found to be an independent predictor of graft loss in pediatric patients [119]. This graft loss seems to be primarily mediated by premature CAV. Increasingly, parvovirus B19 is the virus implicated in US pediatric populations [120]. The use of IVIG is a promising treatment option that seems to mitigate the negative effects of viral infection but requires additional investigation [119].

Conclusion

Heart transplantation remains a widely used approach to patients with end-stage heart failure. Appropriate use of cardiac transplant improves quality of life and extends longevity. However, there are inherent limitations surrounding cardiac transplantation such as donor availability, psychosocial barriers, end-organ function, and contraindications such as fixed PVR. We advocate a multidisciplinary approach to these patients and their families to ensure optimization of care in the pre-, peri-, and postoperative times. Collaboration with Cardiologists skilled in heart failure and transplantation is essential to facilitating this process. Such patients may require extensive stays in the ICU, especially those requiring inotropes or mechanical support. A rigorous and dynamic approach is essential to achieve the greatest outcome.

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Pediatric Lung Transplantation

28

Renee Potera and Charles B. Huddleston

Abstract

Children undergoing lung transplantation present a unique constellation of issues that require compulsive management based upon their underlying diagnosis, state of debilitation, post-transplant needs, and immunosuppression. The ventilator management is also somewhat different from a typically ill child. This chapter will focus on those unique aspects of this group of children with an emphasis on complications seen and the management recommended.

Keywords

Lung transplantation • Surfactant abnormalities • Cystic fibrosis • Pulmonary hypertension

Introduction

The first successful pediatric lung transplant was performed at the University of Toronto in 1987. Since that time, lung transplantation in children has slowly become an accepted therapy for end-stage pulmonary disease of varying causes. Included in this chapter are the most common indications for transplant, as well as common post-operative complications and management in infants and children who have received lung transplants.

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Indications

Cystic Fibrosis

Cystic fibrosis remains one of the leading indications for lung transplantation in children. Of the 1,304 pediatric lung transplants performed from 1990 to 2009, 758 (58 %) were in patients with cystic fibrosis [1]. The decision of when to proceed with transplantation is important, since the current median survival time after transplant is 4.6 years [1], and complications related to transplantation are the second leading cause of death in patients with cystic fibrosis [2]. Several studies have looked to provide physicians guidance in this regard. Karem et al. from the Toronto lung transplant program looked at factors that predicted less than 50 % survival in 2 years [3]. They concluded that patients with an FEV_1 of less than 30 % should be considered for lung transplantation. Robinson [4] suggested that referral should be made for children who have an FEV_1 less than 50 % despite aggressive treatment. Others have found that the rate of decline in the FEV_1 may be more predictive of survival than the absolute percentage, and have recommended patients be referred for transplantation when the expected time for their FEV_1 to be less than 20 % of predicted equals the average waiting time for donor lungs [5].

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Surfactant Protein Abnormalities

These include surfactant protein B deficiency, protein C deficiency and ABCA3 mutations. Surfactant protein B deficiency is an autosomal recessive disorder affecting one per million live births [6]. It generally presents as severe respiratory failure in newborns, unresponsive to aggressive therapy [7]. Unlike surfactant protein B deficiency, surfactant protein C and ABCA3 mutations have variable clinical presentations, and some children do not require transplantation. The outcomes following lung transplantation for surfactant deficiencies are similar to those patients undergoing transplantation for other indications [8, 9].

Pulmonary Vascular Disease

Included in this category are patients with idiopathic pulmonary hypertension, Eisenmenger's syndrome, congenital heart disease and other pulmonary vascular diseases. For patients with idiopathic pulmonary hypertension, death typically occurs as a result of progressive right heart failure [10]. Timing of transplant depends on the patient's response to medical therapy, including intravenous prostacyclin therapy, bosentan and sildenafil, and may possibly be postponed for several years [11]. Lung transplantation in this group of patients is available only if left ventricular function is normal. If left ventricular function is poor, heart-lung transplantation may be required. Right heart function is frequently poor in this group of patients, but frequently returns to normal within a short period of time following transplantation [3].

Eisenmenger's syndrome is characterized by pulmonary hypertension secondary to uncorrected congenital heart disease. Unlike in patients with idiopathic pulmonary hypertension, there are no good prognostic indicators as to when to proceed with transplant. Pulmonary vein stenosis and pulmonary veno-occlusive disease are not easily managed with medical therapies. Stenting and dilation of stenotic veins many provide palliation for some time, but it is recommended that these patients be referred for transplant early. The clinical course of patients with pulmonary hypertension following repair of congenital heart disease is similar to that of patients with idiopathic pulmonary hypertension. Again, the decision to perform isolated lung transplant vs. heart-lung transplant depends on the function of the left ventricle.

Respiratory Failure Following Treatment for Malignancy

Lung transplantation is offered to children following treatment for malignancies provided there is a strong certainty that the malignancy has been completely eradicated [12]. Pulmonary toxicity is a potential complication of several chemotherapeutic agents as well as irradiation and bone marrow transplantation [13–15]. The most common causes of respiratory failure following treatment for malignancies include pulmonary fibrosis and bronchiolitis obliterans. The course of pulmonary fibrosis is highly variable, with some patients having complete resolution following removal of the chemotherapeutic agent, and others progressing to severe respiratory failure [15]. Bronchiolitis obliterans (BO) following bone marrow transplantation is nearly always associated with graft vs. host disease [16], with a 65 % mortality rate at 3 years post-diagnosis [17]. While transplantation in this group of patients is considered high risk, it remains a reasonable option with similar results to those with other indications.

Re-transplantation

Lung re-transplantation in children has been associated with lower rates of survival when compared to primary transplantation [18–20]. In some cases, it remains the only viable option for patients who develop graft failure and BO. Since the survival rates are lower and there are a limited number of donor organs available, patient selection is important. In a recent retrospective study of lung re-transplantation, Scully et al. found that patients who were less than a year post-transplant had worse graft survival, and therefore may not be the best candidates for re-transplantation [21]. Patients who were greater than 1 year post-transplant had similar morbidity and mortality to patients undergoing their first transplant. Further research is needed in this area to determine other factors, if any, that may help refine patient selection to maximize outcomes.

Contraindications to Lung Transplantation

Absolute contraindications to lung transplantation include severe dysfunction of other organ systems or severe systemic diseases. This includes, but is not limited to, malignancy, HIV infection, severe neuromuscular disease, multisystem organ failure and active collagen vascular disease [22]. The presence of certain infections prior to transplant are also considered a contraindication, especially colonization with *Burkholderia cenocepacia* [23, 24].

Relative contraindications include medical issues such as severe malnutrition, poorly controlled diabetes, renal insufficiency, prior thoracic surgery and the presence of antibiotic-resistant microorganisms. Social issues such as psychiatric disturbance in the patient or caregiver and a history of poor adherence with medical therapies are also considered as contraindications. These relative contraindications vary by center [25].

Post-operative Treatment

Immediate Post-operative Management

The patient is transferred from the operating room directly into an isolation room in the intensive care unit. Protective isolation is generally practiced although there are no data to support this. Nonetheless, common sense dictates that health care workers should be particularly cautious in preventing transmitted infections. Many of these patients, particularly those with cystic fibrosis will have multi-resistant organisms necessitating isolation precautions anyway. Hemodynamic monitoring is usually with only central venous pressure line and an arterial line. More invasive monitoring lines such as a Swan-Ganz catheter are generally not necessary and are particularly difficult to manage in small children. Fluid management is of great importance, and a negative fluid balance is the goal within the first 48 h post transplant, given that there is evidence that the newly transplanted lungs are susceptible to the development of pulmonary edema. In a retrospective study in adult lung transplant recipients, a central venous pressure of greater than 7 mmHg was found to be associated with a higher hospital mortality rate and longer intensive care unit stays [26]. However, the need to maintain a negative fluid balance needs to be balanced with the fact that over diuresis places the patient at risk for relatively low cardiac output and renal insufficiency. Generally speaking, these patients do not have very much difficulty with hemodynamic instability. The one exception to this is the group of patients with pulmonary hypertension. Right ventricular dysfunction pre-transplant is very common. Although right ventricular afterload is significantly improved post-transplant, some instability is common, usually requiring low to moderate doses of inotropic agents. There is one cautionary note about patients with Eisenmenger's syndrome who undergo lung transplantation and repair of the cardiac defect (usually a ventricular septal defect). These patients may have acquired right ventricular outflow tract obstruction post-transplant because of the severe right ventricular hypertrophy that accompanies this disease. This occurs presumably as a consequence of the dynamic nature of the outflow tract muscle. At the time of transplantation it is advisable to divide some of the muscle bundles present there and postoperatively avoid high dose inotropic agents.

Within the first 24 h following transplant, a lung perfusion scan is obtained to assess pulmonary blood flow and a bronchoscopy is performed to assess the airway anastomosis. Any major discrepancy in the relative amount of blood flow to each lung should trigger further investigation, usually with cardiac catheterization.

Respiratory care focuses on airway clearance. These patients require aggressive postural drainage and frequent removal of secretions. In order to facilitate pulmonary toilet, adequate pain control is also necessary. Most patients are able to be weaned from mechanical ventilation within a few days following transplant. Delays in the ability to wean from ventilatory support should raise suspicion for possible complications, such as graft dysfunction or phrenic nerve injury.

The vast majority of patients undergoing lung transplantation are malnourished to begin with. It is of paramount importance to establish adequate caloric intake post-transplant. This is complicated by poor intestinal motility that frequently occurs following lung transplantation, which may be related to injury to the vagus nerves during the transplant procedure.

Specific complications and their management will be described in more detail in the following sections of this chapter. The most important complications in the early post-operative period include primary graft dysfunction, rejection and infection. Lung protective ventilation strategies are employed to prevent graft dysfunction. Inhaled nitric oxide is frequently used in the postoperative period for prevention of early graft failure, although some studies have questioned the effectiveness of routine use [27]. Empiric antibiotic therapy is generally targeted at organisms that the patient may have been colonized with prior to transplant. If this information is not available, or if the recipient does not have a significant history of infection, broad-spectrum therapy, such as vancomycin and cefepime, is typically employed. As in all ICU patients, the presence of indwelling catheters places these patients at further risk for infection, and the need for these catheters should be reassessed daily and removed when no longer necessary.

Immunosuppression

Current regimes differ amongst centers, but in general consist of a calcineurin inhibitor, corticosteroids and either mycophenolate mofetil or azathioprine [28]. All these drugs put the patients at risk for infections of a variety of sorts. Corticosteroids have been used for decades for immunosuppression. They inhibit the production of cytokines and also inhibit T-cell growth factor [29]. Side effects include hyperglycemia, hypertension, and with prolonged use, possible skin changes. Cell cycle inhibitors, such as azathioprine and mycophenolate mofetil, are also used as maintenance therapy. These drugs lead to decreases in DNA and RNA synthesis within lymphocytes, therefore affecting their proliferation. Possible adverse effects to this class of medications include myelosuppression and nausea.

Calcineurin inhibitors have been widely used for prophylaxis against rejection in organ transplants. Their mechanism of action is to prevent the synthesis of IL-2 and other cytokines produced by activated T cells [30]. Cyclosporine and tacrolimus are perhaps the most widely used in this group. Adverse

effects noted with these medications are renal toxicity, hypertension, hyperglycemia, seizures and posterior reversible encephalopathy syndrome. They also have several important drug interactions, and require close monitoring of serum drug levels. Sirolimus also binds to the FK-binding protein, but instead of inhibiting calcineurin, the complex it forms inhibits the phosphorylation of the p70s6 kinase, which blocks signal transduction from cell surface cytokine receptors, including IL-2, IL-4, IL-15 and IL-10 receptors [31]. Studies have shown a synergistic effect of sirolimus with cyclosporine [31].

Complications of Lung Transplantation

Infection

Bacterial infections remain a common cause of early morbidity and mortality following transplant. The most common of these organisms are gram-negative pathogens such as *Pseudomonas*, *Klebsiella* and *Haemophilus* spp., but gram-positive organisms such as *Staphylococcus aureus* may also cause pneumonia in the postoperative period. In patients with cystic fibrosis, the causative organism will most likely be the same that colonized the airway prior to transplant. A culture of the donor bronchus is taken at the time of implantation of the organ; occasionally this is a source of infection.

Viral infections are also common, with *Cytomegalovirus* (CMV) being the most common. Patients at highest risk of developing severe primary infection are those who are CMV negative and receive lungs from CMV positive donors [32]. Many centers treat these patients with a prolonged 4–12-week course of ganciclovir. All patients positive for CMV pre-transplant and any receiving an organ from a CMV-positive donor should receive prophylaxis with ganciclovir. The duration of treatment and the route of administration are somewhat controversial. In the absence of need for prophylaxis with ganciclovir, many centers now recommend acyclovir for prophylaxis against herpes simplex infections. The presence of CMV infection, or the detection of the virus in serum or BAL specimens, usually responds to a 14–21 day course of IV ganciclovir. Community acquired respiratory viral infections also lead to significant morbidity and mortality in lung transplant recipients. These include RSV, adenovirus, parainfluenza and influenza infections. Adenovirus is of particular importance, as it has been associated with an increased incidence of early graft failure and death [33]. The treatment for most community acquired viral infections is supportive, although some centers use intravenous or inhaled ribavirin in severe cases [34, 35]. Some current recommendations include using acyclovir for prophylaxis against herpes simplex viral infections in patients who do not require prophylaxis with ganciclovir.

Fungal infections can occur as well, with the most common organisms being *Aspergillus* and *Candida* species. The identification of both of these organisms may represent colonization, but due to the potential of invasive disease, treatment should be considered. *Candida albicans* is frequently identified post transplant, and can cause invasive disease [36]. Invasive *Aspergillus* disease has a mortality rate up to 60 % in lung transplant recipients [37]. Risk factors for the development of invasive fungal diseases include colonization with these organisms prior to transplant, especially in patients with cystic fibrosis [38]. Treatment depends on the organism identified and the sensitivity patterns. For *Candida albicans*, treatment with fluconazole is generally effective. For non-albicans species, voriconazole is usually effective. Amphotericin B has been the drug of choice for treatment of invasive *Aspergillus*, although capsofungin is a reasonable alternative. Voriconazole in particular has significant drug interactions with immunosuppressive medications, so careful monitoring is needed.

Graft Complications

Primary Graft Dysfunction

Primary graft dysfunction (PGD) is the leading cause of early mortality after lung transplantation. Also known as early graft dysfunction or severe ischemia-reperfusion injury, it has a reported incidence of between 11 and 25 % [39–41]. PGD generally occurs within the first 24 h after transplantation, with a clinical picture similar to that of acute respiratory distress syndrome (ARDS). In attempts to consistently describe the severity of PGD, a grading system was proposed from the International Society of Heart and Lung Transplantation in 2005. This classification grades the severity of PGD from 0 to 3 based on PaO_2/FiO_2 ratio and the presence or absence of radiographic abnormalities. Absence of infiltrates on chest radiographs (CXR) is rated as grade 0 regardless of PaO_2/FiO_2 ratio. If this ratio is greater than 300, but there are infiltrates on the CXR, it is grade 1. Grade 2 includes PaO_2/FiO_2 between 200 and 300 with CXR abnormalities, and Grade 3 has a PaO_2/FiO_2 ratio less than 200. Any patient on extracorporeal oxygenation is classified as grade 3 [42]. The practical utility of this classification system is marginal in part because of the changing nature of blood gases and chest radiographic findings in the first 48 h post-transplant.

Treatment of PGD includes the use of lung-protective ventilation, maintenance of a negative fluid balance, and pulmonary vasodilator therapy [43]. In severe cases, ECMO has been utilized, with varying results. In adults, there are several case series reporting 1-year survival rates from 26 to 47 % when ECMO has been used post-operatively, predominately for PGD [44–48]. In children, 1-year survival rates range from 28 to 41 % with ECMO for PGD [46, 49], with suggestion that earlier ECMO support may lead to improved

outcomes for this indication [49]. The improved results with earlier implementation of ECMO is likely related to avoidance of barotrauma associated with high ventilator pressures necessary to maintain satisfactory ventilation in the presence of significant lung dysfunction.

Rejection

Patients who are candidates for lung transplantation have extensive pre-transplant testing to assess risk of antibody-mediated rejection. This includes assessment of the Panel Reactive Antibody (PRA) and crossmatch results. The PRA is determined by assessing what percentage of lymphocytes in a stored panel of known HLA types that are recognized by the recipient's antibodies. Patients with a positive PRA are considered high-risk for acute rejection, with decreased survival post-transplant as the PRA increases [50]. Crossmatching is performed by incubating serum from the recipient with leukocytes from the donor to assess real-time antibody binding. Since this is often impractical, a "virtual crossmatch" is often performed instead, by comparing antibodies known to be present in the recipient with donor antigens [50]. Patients with a positive cross-match are treated with IVIG and plasmapheresis.

Antibody-mediated rejection has been recognized as a cause for hyperacute rejection, but is more recently gaining recognition in acute and chronic rejection as well. Hyperacute rejection is due to preexisting antibodies in the recipient that interact with donor antigens. Pathologically, it is identified by the presence of small vessel vasculitis and necrosis and diffuse alveolar damage, with capillary congestion with neutrophils and antibody deposition on endothelial surfaces [51]. The diagnosis of acute and chronic antibody mediated rejection is more difficult, with a lack of consensus as to the pathologic appearance of humoral rejection. The presence of circulating antibodies with or without specific biopsy findings may represent latent or silent rejection, but is of unclear clinical significance [52].

Acute cellular rejection may affect up to 55 % of lung transplant recipients in the first year following transplantation [53], and is defined based on the histologic appearance of lung allograft tissue. While episodes of acute rejection may be symptomatic, presenting with cough, dyspnea, hypoxia and fever, many episodes are diagnosed in asymptomatic patients undergoing routine surveillance. In patients who are able to perform pulmonary function testing, the decline in the FEV1 has been found to have a sensitivity of about 60 % for detecting infection or rejection grade A2 and higher, but can not distinguish between the two [54]. Some studies have demonstrated that the findings of ground-glass opacities, volume loss and pleural effusions on high-resolution chest computed tomography indicate acute rejection, but more recent data indicates a very low sensitivity of 35 % for these findings [55].

Bronchoscopy with transbronchial biopsies remains the most important method by which to diagnosis rejection. The procedure itself is relatively safe, with possible complications including transient hypoxemia, small volume bleeding, pneumothorax and arrhythmia, all occurring at low rates, with no mortality reported [56, 57]. Most biopsies are obtained from the lower lobes, since if rejection is present, the grade has been shown to be worse in the lower lobes as compared to the upper lobes [58].

Bronchoscopy is also performed as surveillance to diagnose asymptomatic rejection in patients post-transplant. Acute rejection has been detected in 6.1–39 % of routine surveillance bronchoscopies [56, 59]. Although varying monitoring strategies are currently in use, there has never been a randomized clinical trial comparing different strategies. With the incidence of acute rejection being the highest in the first year after transplant, many centers perform routine bronchoscopies at 1 month, 3 months, 6 months and then on an annual basis [60].

Treatment of episodes of acute rejection consists of increased immunosuppression. In general, the treatment for acute rejection is pulse-steroids, usually consisting of at least 3 days of high-dose steroids IV followed by an oral taper, which has been proven effective in several studies [61, 62]. Plasmapheresis is the treatment of choice for antibody-mediated rejection. Intravenous immunoglobulin (IVIG) is another common therapy, leading to B cell apoptosis, down regulation of B cell surface antigens, and inhibition of complement activation. Anti-CD20 monoclonal antibodies, such as Rituximab, also deplete B-cells and have been effective in treating presensitized kidney transplant recipients [63–65].

Bronchiolitis obliterans (BO) is thought to be a manifestation of chronic rejection, occurring in about 50 % of patients following lung transplantation [66]. It is a pathologic process characterized by partial or complete obstruction and destruction of distal airways. Several risk factors have been identified in the development of BO following lung transplantation, including recurrent episodes of acute cellular rejection, gastroesophageal reflux disease (GERD), and viral infections. Regardless of the underlying cause of BO, the prognosis is poor. Several studies have found the 3-year survival of patients with BO to be about 51 % [67–69]. Treatment plans for post-transplant BO are variable, but usually includes altering immunosuppression, either by changing agents or adding additional agents. There is evidence that changing from cyclosporine to tacrolimus [70, 71], or adding either mycophenolate mofetil [72] or sirolimus [73] to the current immunosuppressive regime may be helpful. Other therapies, such as extracorporeal photopheresis, have been used with variable results [74, 75]. Still other medications, such as azithromycin, which has anti-inflammatory effects [76] and clotrimazole, which may decrease the proliferation of fibroblasts [64], have not had formal clinical trials to evaluate effectiveness in treating BO. In many cases, re-transplantation is a strong consideration.

Airway Complications

The bronchial anastomosis in lung transplantation is at risk for a variety of complications. This is largely due to the fact that there is no direct blood supply to the bronchus. Normal lungs have a dual blood supply, with the bronchial blood flow arising from the intercostal arteries or directly from the descending aorta. During lung harvest, the bronchial artery circulation is lost, and revascularization may take up to 2–4 weeks [77]. Circulation to the donor's bronchus during this time is dependent on the retrograde filling of bronchial arteries by the pulmonary arteries.

The reported incidence of airway complications varies. Possible airway complications include bronchial dehiscence, bronchial stenosis, granulation tissue formation, bronchial fistulas and tracheo-broncho-malacia. With recent surgical advances in the field, bronchial dehiscence, while once the major source of early morbidity and mortality, has become a relatively rare complication. Bronchial stenosis is the most common airway complication, with a reported incidence ranging from 2 to 32 % [78, 79]. Balloon dilatation using a rigid bronchoscope is typically the treatment of choice. Occasionally stent placement may be necessary. Although the incidence of bronchial anastomotic stenosis is the same for infants as it is for teenagers, small infants have a higher incidence of native tracheo-bronchomalacia in the native airways. This may complicate ventilator weaning.

Vascular and Nerve Complications

Vascular anastomosis complications are also rare. A lung perfusion scan is typically performed within 24 h of transplant to screen for such complications. More common complications include phrenic nerve injury, injury to the recurrent laryngeal nerve and bleeding. Phrenic nerve dysfunction is relatively common, with a reported incidence ranging from 9.3 to 29.6 % [80, 81]. This complication has been found to be more common on the right side, and diaphragmatic dysfunction can be confirmed by fluoroscopy or ultrasound [80, 82].

Other Complications

Atrial flutter has been observed following lung transplantation. This is thought to be secondary to suture lines placed in the left atrium during pulmonary venous anastomosis [83]. Type 1 antiarrhythmic medications have been shown to be effective for treatment if this complication should occur [83].

Impaired gastric motility and GERD are common after lung transplantation [84], and may be exacerbated by iatrogenic vagal nerve injury and the use of calcineurin inhibitors [85, 86]. In addition, an impaired cough reflex following transplantation may increase the risk of aspiration. Some studies have demonstrated improved survival in patients without reflux [87], and prophylactic fundoplication may decrease the incidence of BO in transplant recipients [87–89]. Further studies are needed to determine the long-term benefit of such therapies.

Post-transplant lymphoproliferative disease (PTLD) is another possible complication, occurring in about 10 % of patients, and is associated with primary Epstein-Barr virus infection [90]. Therapy for PTLD includes reduction in immunosuppression, anti-CD20 antibodies, or chemotherapy [25].

Survival

The 5-year survival rate from 1990 to 2008 in pediatric lung transplantation is 48 % [1]. When analyzing the data from 2002 to 2008, the 5-year survival is 52 %, mostly due to improved early survival [1]. Survival is the same for all patients, regardless of pre-transplant diagnosis. The leading cause of death remains to be BO, with infection and graft failure also significant causes. Clearly, better understanding and treatment of BO may improve survival considerably.

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Pediatric Liver Transplantation

29

Denis Devictor and Pierre Tissieres

Abstract

Pediatric Liver Transplantation (LT) is one of the most successful solid organ transplants with long term survival more than 80 %. Nowadays, pediatric liver transplantations in children are routinely performed in all developed countries across the world and the acquired experience is considerable. This success is dependent on constant collaboration between pediatricians, hepatologists, surgeons, intensivists, nurses, transplant coordinators, dieticians, psychologists and social workers. Many aspects have contributed to improve survival in children post-LT, especially advancements in pre-, peri-, and post- transplant management. The development of new surgical techniques, such as reduction hepatectomy, split-LT and the introduction of living related LT, has extended LT to infants under the age of 1 year and even in neonates. Progress in the last 20 years has also been characterized in large part by the introduction of calcineurin inhibitors, cyclosporine and tacrolimus that today represent the keystone of most immunosuppressive protocols. One major problem remains the lack of donors. Donation after cardiac death offers a new possibility to increase the pool of potential donors. In children with acute liver failure, increasing interest has centered on the possibility of providing temporary liver support based on extracorporeal devices (artificial and bioartificial) or on hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it. Similarly, hepatocyte transplantation offers new perspective in infants and children with metabolic failure. As long-term survival increases, attention has now focused on the quality of life achieved by children undergoing transplantation.

Keywords

Liver transplantation • Liver graft • Children • Neonates • Biliary atresia • Cholestatic diseases • Acute liver failure • Metabolic diseases • Immunosuppression • Surgery • Results • Outcome

Introduction

Pediatric liver transplantation (LT) is one of the most successful solid organ transplants [1–3]. It has become a well-established and successful strategy in treating children with end-stage liver disease as well as children with irreversible acute liver failure, with excellent success and limited mortality. In most centers, the 1-year actuarial survival rate is higher than 90 % in elective patients and higher than 70 % in children with acute liver failure [4]. Long-term survival is also excellent – more than 80 % of children will survive to become teenagers and adults with

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Table 29.1 Indications for liver transplantation in children and outcomes

	Frequency (%)	
	SPLIT registry[a]	BICETRE
Diagnosis	1995–2002	1986–2002
Number of patients	n = 1092	n = 568
Number of transplantations	NA	648
Cholestatic liver disease	66 %	77 %
Biliary atresia	42 %	53 %
Others	14 %	34 %
Alagille syndrome		6 %
Sclerosing cholangitis,		3.5 %
Progressive familial intrahepatic cholestasis		8 %
Alpha-1-antitrypsine deficiency		4.5 %
Acute liver failure	13 %	11 %
Metabolic diseases	12 %	9 %
Others	13 %	3 %
Liver graft survival	75 %[b]	65 %[c]
Patient survival	69 %[b]	83 %[c]

SPLIT Studies of pediatric liver transplantation, *NA* not available
[a]Data from Ref. [3]
[b]15-year outcome
[c]3-year outcome

excellent health-related quality of life [5–7]. Many aspects have contributed to improved survival in children post-LT, especially advancements in pre-, peri-, and post- transplant management [8]. The development of new surgical techniques, such as reduction hepatectomy, split-LT and the introduction of living related LT, has extended LT to infants under the age of 1 year and weighing less than 8 kg, which has effectively reduced the waiting list mortality from 25 to 5 %. Nowadays LT in children are routinely performed in all developed countries across the world and the acquired experience is considerable. Reports of experience from single centers provide are certainly encouraging, and the databases of the Studies in Pediatric Liver Transplantation (SPLIT group) and of the pediatric acute liver failure study group (PALF group) are also invaluable sources demonstrating these marked improvements in outcome [5, 9–11]. For instance, the data of the SPLIT group allows analysis of currently more than 4,000 North-American children who have undergone LT [12–15]. Similarly, the PALF group provides considerable data to improve our understanding on the treatment and outcome of children with acute liver failure and to identify factors to predict need for LT in children with ALF [10].

Indications for Liver Transplantation

The main indications for LT in the pediatric population can be broadly separated in four groups: cholestatic liver diseases, acute liver failure, metabolic liver disease, and liver tumors (Tables 29.1 and 29.2) [1, 16].

Table 29.2 Patient characteristics of 2,982 children who underwent a first liver transplantation registered in SPLIT from 1995 to 2008

	Total N = 2982	
	N	%
Age at transplant		
Missing	1	0.0
0–6 month	260	8.7
6–12 month	725	24.3
1–5 year	962	32.3
5–13 year	616	20.7
13 + year	418	14.0
Race		
Missing	47	1.6
White	1668	56.3
Black	464	15.6
Hispanic	494	16.6
Other	299	10.0
Sex		
Missing	1	0.0
Male	1407	47.2
Female	1574	52.8
Primary disease		
Biliary atresia	1203	40.3
Other cholestatic or metabolic	837	28.1
Fulminant liver failure	420	14.1
Cirrhosis	1996	6.6
Other	326	10.9
Patient status at transplant		
Missing	15	0.5
ICU/intubated	369	12.4
ICU/non intubated	407	13.6
Hospitalized	514	17.2
Home	1677	56.2

Based on data from Ref. [10]

Cholestatic Liver Disease

Biliary atresia is the most common cause of chronic cholestasis in infants and accounts for nearly 50 % of the indications for LT in children. Most of these small children have undergone a Kasai procedure that failed to re-establish effective biliary flow. Consequently, they develop secondary biliary cirrhosis leading to chronic end-stage liver failure. Out of 1187 children transplanted in North America between 1995 and May 2002, 33.5 % were ≤ 12 months old at the time of transplantation, 55.6 % had cholestatic disease, and 41.6 % had biliary atresia. Of the children transplanted at < 1 year of age, 65.6 % had biliary atresia [17]. Indications for LT in children with biliary atresia are cholangitis or progressive jaundice (35 %), portal hypertension or hepatorenal syndrome (41 %), and decreased liver synthetic functions. Intrahepatic cholestasis such as sclerosing cholangitis, Alagille's syndrome, non-syndromic paucity of intrahepatic bile ducts, and progressive familial intrahepatic cholestasis represent approximately 15 % of all transplantations [11].

Table 29.3 Causes of ALF in infants and children admitted at the Bicêtre Hospital PICU (1986–2007) and compared to those reported by the PALF[a] study group

Causes		Infants <1 year (n = 107)	Children ≥1 year (n = 128)	Total (n = 235)	Infants <7 month (n = 149)	≥ 1 year ≥7 month (n = 554)	Total (n = 703)
Infectious	HAV, HBV, herpes simplex, HHV6, EBV, enterovirus, adenovirus, parvovirus B19, dengue fever	19 (18 %)	33 (26 %)	52 (22 %)	20 (13 %)	25 (4 %)	45 (6 %)
Undetermined		10 (9 %)	32 (25 %)	42 (18 %)	61 (49 %)	268(48 %)	329 (47 %)
Toxic	Acetaminophen, sulfamide, sodium valproate, sulfasalazine, halothane, amanita phalloides, chemotherapy	7 (7 %)	25 (19 %)	32 (14 %)	3 (2 %)	108 (19 %)	111 (16 %)
Autoimmune	Giant cell hepatitis, LKM or LC1 autoimmune hepatitis	8 (7 %)	7 (5 %)	15 (6 %)	0 (0 %)	48 (9 %)	48 (7 %)
Hematologic	Familial lymphohistiocytosis, macrophage activation syndrome, leukemia	7 (7 %)	3 (2 %)	10 (4 %)	–	–	–
Vascular	Veno-occlusive disease, Budd Chiari syndrome	2 (2 %)	1 (1 %)	3 (1 %)	–	–	–
Other	Ischemic liver	–	–	–	38 (25 %)	64 (12 %)	102 (14 %)

Based on data from Ref. [24]
HAV hepatitis A virus, *HBV* hepatitis B virus, *HHV* human herpes virus, *EBV* Epstein-Barr virus, *LKM* liver kidney microsome, *LC1* liver cytosol 1
[a]PALF: Pediatric Acute Liver failure study group adapted from Refs. [11, 12]

Metabolic Diseases

Metabolic diseases are the second most common indication for LT [18–22]. They include primary hepatic diseases such as Wilson disease, alpha-1-antitrypsin deficiency, and cystic fibrosis, as well as primarily nonhepatic diseases such as ornithine transcarbamylase deficiency, Criggler-Najjar syndrome type 1, primary hyperoxaliuria type 1, and organic academia. In children with primary hyperoxaluria type I, combined liver and kidney transplantation should be considered when irreversible renal injury from oxalic acid accumulation has developed. Liver transplantation has been recently suggested for the treatment of organic acidemia (propionic aciduria, methylmalonic aciduria) as well. However, LT does not correct the enzyme deficiency in other organs except the liver, and patients remain at risk of severe extra-hepatic complications. Children transplanted for metabolic diseases generally have excellent outcomes [18, 20, 21].

Acute Liver Failure

Acute liver failure (ALF) accounts for approximately 10 % of all LTs in children [23–26]. The causes of acute liver failure are age-dependent (Table 29.3). For example, in neonates and infants the main causes are viral infections and inborn metabolic disorders, whereas in children the main causes are drug-induced acute liver failure, autoimmune hepatitis and viral infections [10, 23, 24, 27]. However, in around 50 % of the cases, the cause of acute liver failure cannot be determined. This high proportion of undetermined acute liver failure can be explained because a significant number of these cases have undergone an incomplete screening, especially regarding metabolic diseases and autoimmune liver disease [24, 25]. Graft survival in children with acute liver failure is significantly lower than that of children transplanted for other causes [24, 28]. Grade 4 encephalopathy, age < 1 year, and dialysis before transplantation are risk factors for poor outcome [29]. In children with acute liver failure, increasing interest has centered on the possibility of providing temporary liver support with extracorporeal devices (artificial and bioartificial) or with hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it [30].

Other Indications

Liver tumors are mainly represented by hepatoblastoma. Children with hepatoblastoma should first be treated with chemotherapy and then evaluated for resection or transplantation [31, 32]. Hepatocellular carcinoma in children is rare and is often secondary to another chronic underlying disease liver disease. The development of hepatocellular carcinoma has been reported in greater frequency in children with biliary atresia, Alagille's syndrome, progressive intrahepatic cholestasis, and tyrosinemia. In children with tyrosinemia, there was a 33 % incidence of hepatocellular

carcinoma before 2 years of age that seems to be reduced if not eliminated by 2-(2-nitro-4-3 trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) therapy [16].

Contraindications to Liver Transplantation

The list of contraindications to LT in children has been shortened considerably because surgical techniques and medical management have improved significantly over time [1]. Absolute contraindications to pediatric LT are conditions in which LT is futile therapy: (1) unresectable extrahepatic malignant tumor considered incurable by standard oncologic criteria; (2) concomitant end-stage organ failure that cannot be corrected by a combined transplant; (3) uncontrolled systemic infection or multiple organ failure, and (4) irreversible serious neurological damage. Relative contraindications include malignancy that is considered cured or curable by standard oncologic criteria and treatable infection. Obviously the contraindications should be discussed on a case-by-case analysis.

Evaluation of Potential LT Recipients

The appropriate selection and evaluation of potential LT recipients is crucial to achieving good outcomes [1, 16]. The primary goal of the evaluation process is to identify appropriate candidates for LT. The first step is to determine whether LT remains the best option and that no other medical therapies could be life sustaining with adequate quality of life. Contraindications should be identified at this stage of the evaluation process. Once the indication is confirmed, the second step is to determine the severity of the disease and assess for any complications or co-morbidities.

In the ideal situation, LT would be offered before the onset of life-threatening complications. To determine the degree of severity of liver disease, the medical screening requires specific blood tests, radiologic evaluation, and consultations with specialists. The major functions of the liver can be grouped into four general categories: (1) protein synthesis, (2) bile formation and excretion, (3) immunologic functions, (4) and hemodynamic functions. All these functions are assessed with appropriate laboratory and radiologic exams. The laboratory tests include exposures to viral infections (cytomegalovirus, Epstein-Barr virus in particular). Radiologic evaluation should identify vascular anomalies or portal vein thrombosis. Radiologic evaluation includes a Doppler ultrasound and may also require magnetic resonance imaging or computed tomography angiography. Assessment for extrahepatic disease that might impact on peri-, per-, or operative management is an important part of the evaluation, and will vary with the underlying disease. Children with Alagille syndrome for instance, require careful cardiac and renal assessment, since these organs are involved in this syndrome.

The second goal of this evaluation is to establish a pre-transplant program. The importance of nutritional support at every stage of the management of liver disease should be stressed, since growth impairment has been associated with longer post-transplant hospital stays [33]. The pre-transplant therapeutic plan also includes immunizations, prevention or treatment of drug-induced side effects, education and support to the patient and family (especially to inform and educate both the parents and the child if possible, on LT procedure and on the post-operative period), and evaluate social status and logistic issues. Preparation of the recipient and family for LT is a key issue requiring the constant collaboration between the primary care practitioner, pediatricians, hepatologists, surgeons, nurses, transplant coordinators, dieticians, psychologists and social workers. The collaboration with the primary care practitioner is crucial particularly to optimize the communication between the patient and family with the transplant team, to complete and often accelerate immunization schedules before transplantation, and to optimize nutritional support and detect potential complications [1].

Prioritization

In most countries with an established organ transplantation network, graft allocation is based on the concept that organs need to be allocated to the sickest patients. Most systems preferentially allocate pediatric donors to pediatric recipients. However, the policy to allocate organs is undergoing constant adaptations and modifications because of a persistent donor shortage. In the United States, the PELD score was introduced in 2002 to stratify the degree of illness in children with similar diseases who are competing for pediatric liver grafts. This score is calculated from a formula based on objective medical criteria including total bilirubin (mg/dL), INR, serum albumin (g/dL), age less than 1 year, and growth failure (height less than 2 standard deviations from the mean for age and gender) [1, 16, 34–36]. Additional PELD points are awarded for specific risk factors not taken into account in the PELD score, such as hepatopulmonary syndrome, metabolic diseases, and liver tumors. The adoption of the PELD score in the USA has improved the access and accountability of the allocation system. Since the use of the PELD score, fewer children are now dying on the waiting list [1, 35]. However, the PELD score does not cover all pediatric situations [1]. It is currently used only for children up to 12 years old, does not take into account potential complications of end-stage liver disease (hepatopulmonary syndrome for instance), and is not adapted to children with acute liver failure, liver tumors or metabolic diseases.

The Transplant Operation

It is not possible to review all the surgical aspect of LT, however it is important for pediatric intensivists to have a basic understanding of the processes involved in harvesting the organ from the donor and transplanting it to the recipient. The technical aspects of the arterial reconstruction, the portal vein anastomosis, and the restoration of biliary tract continuity are important to consider for the pediatric intensivist as each procedure has its own share of complications. Therefore the communication between the surgeons, radiologists and intensivist is crucial during the peri and post-operative period.

Allograft Procurement

Donor Selection

Selection of an appropriate liver donor is vitally important to the short and long-term success of the transplantation. Particular attention is paid to donor age, cause of brain death, intensive care hospitalization time, infections, and presence of hemodynamic stability. No consistent data exist on the effect of donor age on the long-term results of pediatric LT. Up to the early 1980s, the only technical option was to transplant the whole liver of a donor with a weight as close as possible to that of the recipient. However, the shortage of pediatric cadaveric donors has resulted in a high mortality rate on the waiting list. The development of techniques that allow surgeons to transplant portion of livers from adult donors has expanded the donor pool and has been a major advancement in reducing the waiting period and improving the survival rates of pediatric LT. Currently reduced-liver grafts to the left lateral segments and split livers provide the majority of grafts in infants, whereas left or right lobes are used in older recipients (Table 29.4).

Table 29.4 Transplant characteristics of 2,982 children who underwent a first liver transplantation registered in SPLIT from 1995 to 2008

	Total N = 2982	
	N	%
Donor organ		
Missing	100	3.4
Live	461	15.5
Whole	1564	52.4
Reduced	482	16.2
Split	375	12.6
Transplant year		
1995–2001	1161	38.9
2002–2008	1821	61.1
Primary immunosuppression		
Missing	128	4.3
Ciclosporine	444	14.9
Tacrolimus	2326	78.0
Other	84	2.8
Donor age		
Missing	213	7.1
0–6 month	148	5.0
6–12 month	121	4.1
1–18 year	1482	49.7
18–50 year	932	31.3
≥ 50 year	86	2.9

Based on data from Ref. [10]

Whole-Liver Transplantation

To date, whole-organ transplantation is used when a cadaveric donor has an approximate recipient size. When using whole-organ grafts, the donor weight should range 15 % above or below that of recipient. Occasionally, abdominal-wall closure may be difficult because of the large size of the liver graft. The subsequent risk is the development of an abdominal compartment syndrome. This may be remedied by the use of a silastic prosthesis on the abdominal wall so that a temporary closure can be made.

Reduced-Size Liver Transplantation

This procedure consists in the procurement of the whole liver from an adult cadaver donor, which is reduced in its size. According to the original description, a right hepatectomy is performed and the left lobe (segments I to IV) is transplanted in a child. This technique allows surgeons to overcome differences in size between the donor and the recipient of up to four or five times. More extended reductions of the graft – for example, only keeping the segments 2 and 3 are also possible, allowing transplantation of liver from donors with a body weight up to 12 times the recipient's one. Estimates of donor graft-to-recipient body weight ratio (optimal between 1.5 and 3 % or 150–200 g, for a recipient who weighs 10 kg) appear to be the most accurate predictor of adequate graft volume. Reduced-size liver transplantation shows similar outcomes to whole-liver transplantation [3, 12, 15, 37, 38]. However, this procedure reduces the pool of liver for adults. Therefore, other option such as split liver and living-related liver transplantation have been developed.

Split-Liver Transplantation

Split-liver transplantation allows two functional allografts. The left lateral segment (segment 2 and 3) is transplanted in a child, whereas the right liver is transplanted into an adult. This procedure increases the ischemia time, with an increased risk of primary dysfunction and technical complications. Because split-liver transplantation may require a prolonged ischemic period, selection of donor patients is crucial [16]. However, the possibility to split the liver in situ can reduce the ischemia time. This procedure has shown comparable results to those obtained with conventional techniques.

Living-Related Liver Transplantation

Living-related liver transplantation accounts for a substantial number of pediatric LT performed in many centers across the world and the only possibility for LT in countries where cadaveric organ procurement was not allowed [39]. The procedure consists in a left lobectomy during which segments 2 and 3 are separated from the remaining liver. Living-related liver transplantation has been widely debated with regard to the ethics of performing major surgery on a healthy person. Donor mortality and morbidity is estimated at approximately 0.2 and 10 % respectively. Evaluation of the donor and the recipient is crucial. Recipient size and age are important, because there is evidence that infants and small children do better than older children with living donor transplantation [40]. In the majority of cases, living related transplants register an excellent outcome for pediatric patients, thanks to the possibility of performing the transplant before the child's clinical condition deteriorates. Living-related liver transplantation should also be considered in children with acute liver failure when no cadaveric grafts are available.

Recipient Procedure

Most liver transplants follow the similar order [16]. The details of the recipient operation cannot be described here. They have been described elsewhere [32]. In brief, LT has three major phases. The first one begins with the recipient hepatectomy. It is often the most difficult part of the procedure because of complicating features (portal hypertension, coagulopathy, and adhesions from prior surgery). The second phase is the anhepatic phase. The graft is placed starting with the vascular outflow anastomosis first, including the hepatic veins and infrahepatic vena cava, followed by the vascular inflow of the portal vein and finally hepatic artery. Following the neo-liver perfusion, the initial blood return to the heart is necessarily cold, acidotic, and hyperkalemic caused by cold perfusion techniques. Significant cardiovascular instability can result in additional hemostatic problems caused by coagulopathy and fibrinolysis. The specialized anesthesia team should be prepared to manage these problems. The biliary anatomosis is performed in the final phase. A Roux-en-Y anastomosis (hepaticojejunostomy) is obviously necessary in patients undergoing LT for biliary atresia. This approach is also used in young children receiving a segmental graft, those with an abnormal native biliary tree, as in sclerosing cholangitis, or if the donor or recipient duct is very small. A direct choledocho-choledochostomy is possible in other patients with a normal native biliary tract.

The operative procedure is marked by important issues, which may influence postoperative management. Severe portal hypertension may result in critical bleeding during removal of the native liver. Bleeding may occur during dissection of extensive adherences, such as in children with biliary atresia who underwent previous portoenterostomy surgeries. Assessment of vascular anastomosis is essential; for example, portal anastomosis in children with biliary atresia may be difficult, as portal vessels are frequently hypoplastic. Arterial anastomosis may preclude important dissection along the infrarenal aorta, with subsequent risk of traumatic lesions to the pancreas. The appearance of the liver graft after unclamping may be informative regarding the quality of the graft. Finally, abdominal closure should be performed in a manner to avoid increased intra-abdominal pressure.

Management During the Early Postoperative Period

After transplantation, children are taken to the PICU for intensive care monitoring and management. Management can be divided into two main issues: the general management of a patient after major abdominal surgery and, specific considerations regarding liver transplantation.

General Post-operative Management

Respiratory

Patients should be weaned from the ventilator and extubated as soon as possible, because prolonged mechanical ventilation has been associated with higher mortality and morbidity. In general, children can be extubated within 1–4 days after transplantation. However, for some children, a more prolonged course of mechanical ventilation is necessary because of increased abdominal pressure, malnutrition, postoperative pain, or other complications such as sepsis, liver dysfunction, refractory ascites, and in rare cases, right phrenic nerve paresis. A daily chest radiograph should be obtained to assess for atelectasis and effusions. Pleural effusions secondary to ascites passing across the diaphragm are common and can be treated with diuretic therapy. In some cases, a pleural pigtail catheter is required. Continuous monitoring of oxygen saturation and expired carbon dioxide, and frequent assessment of arterial blood gas values should also be performed.

Cardiovascular

Continuous arterial pressure and central venous pressure should be monitored. The abdominal catheter drainage should be assessed every hour for extensive bleeding indicating possible hemorrhage from the vascular anastomosis, or coagulopathy, especially in case of primary non-function. Hypotension may be the result of intra-abdominal bleeding, sepsis, or volume depletion. Hypertension may be the results of side effects from immunosuppressive agents, volume overload, or pain.

Gastrointestinal

It is crucial to assess synthetic, metabolic, and excretory function of the graft immediately after transplantation. Absence of intra-abdominal bleeding, and rapid correction of coagulation abnormalities are the best indicators of synthetic function. Adequate metabolic function is reflected in normalizing lactate levels, and if the child is awakening within several hours following the transplant procedure. Clearance of anesthesia is a good indicator of synthetic function. After 48 h, the total bilirubin, coagulations tests, and transaminases are reliable indicators of liver function. Depending upon the degree of graft injury due to ischemia, the transaminases' levels skyrock within 2 days and should be near normal after 7 days.

Renal

Electrolytes and fluid balance should be monitored closely. Massive fluid shifts from ascites, blood loss, and stress from major surgery may occur resulting in hypovolemia, hypotension, metabolic and electrolyte disturbances. With the addition of nephrotoxic drugs, such as tacrolimus and some antibiotics, patients are at higher risk of kidney impairment.

Neurologic

Level of consciousness is an important indicator of graft function. Graft dysfunction is generally indicated by slowness to waken.

Table 29.5 Indications for retransplantation of the liver

Primary non-function	22 %
Chronic allograft rejection	21 %
Hepatic artery thrombosis	18 %
Portal vein thrombosis	17 %
Acute allograft rejection	7 %
Atypical acute allograft rejection	6 %
Biliary complications	3 %
Recurent or de novo viral diseases	5 %
Other	1 %

Based on data from Ref. [41]

Specific Post-operative Considerations

Specific post-operative management of the liver transplant patient includes monitoring for both surgical and medical complications. Surgical complications have reduced over time, but sepsis and rejection remain significant issues (Tables 29.5 and 29.6).

Surgical Considerations

Primary Non-function and Sub-function of the Graft

Primary non-function of the graft is a rare but catastrophic event. It usually occurs within the first 48 h following the procedure, and diagnosis is based on absence of neurologic awakening, hepatic encephalopathy, bleeding, increasing liver enzymes, lactic acidosis, and vasoplegic shock. In cases of split-liver transplant, information regarding the other liver recipient's postoperative course may help in diagnosing primary graft non-function. The only therapy is emergency re-transplantation. Sub-graft function with persistent coagulopathy is also possible but generally reversible within a few days. Although the cause is unknown, it is likely the result of the donor rather than recipient factors and probably related to ischemia/reperfusion injury of the graft, which further emphasizes the critical importance of the donor's selection

Table 29.6 Specific post-operative complications after liver transplantation in children

Ref	Year	Liver transplantation N	HAT	PVC	HV stenosis	Biliary complications	Digestive complications
Bourdeaux et al. [42]	2007						
Total		235	7.6	9.4	1.7	21.7	NA
LRDT		235	1	13	0	30	
Kim et al. [43]	2005						
Total		170	7	1.8	NA	7	3.5
LRDT		51	4	2		6	4
Fouquet et al. [6][a]	2005	280	17	11	NA	20	13
Diamond et al. [12][b]	2007						
Total		2192	7.6	5.5	NA	12	9.8
LRDT		360	6.7	7.5		17.5	11.1
Ueda et al. [44][c]	2006	600	3.3	7.5	3.7	14.5	5.7
Heaton et al. [45][c]	2008	50	6	4	NA	14	

LRDT living related donor transplantation, *HAT* hepatic artery thrombosis, *PVC* portal vein complication (thrombosis or stenosis), *SHV* stenosis, stenosis of the hepatic vein anastomosis

[a]Liver transplantation only for biliary atresia

[b]Complication occurring within the first month after transplantation

[c]Living related liver transplantation only

(cause of cerebral death, hemodynamic stabilities, normoxia, age, etc.), as previously mentioned.

Vascular Complications

Vascular thrombosis is the main postoperative complication that will cause graft loss. Hepatic artery thrombosis occurs in children (5–15 %) three times more frequently than in adults, usually within the first 30 days after transplantation [3, 14]. This complication is directly related to the size of the vessels and thus is most likely in the smallest pediatric recipients and/or small liver grafts [46]. Prevention of hepatic artery thrombosis in these situations is based on anticoagulation, antiplatelet aggregation therapy, and avoiding hemoconcentration. Hepatic artery thrombosis can occur with various clinical presentations, which may include acute allograft failure, biliary obstruction, or sepsis. Suspected hepatic artery thrombosis requires prompt evaluation with duplex sonography, magnetic resonance angiography, or angiogram. Successful thrombectomy is possible if hepatic artery thrombosis diagnosis is made before graft necrosis occurs. Hepatic artery thrombosis can also occur as a late complication and can manifest as biliary strictures, bilomas, or sepsis. These biliary complications are particularly frequent after hepatic artery thrombosis because the hepatic artery offers most of the vascularization to the bile duct. In case of biliary tract necrosis due to hepatic artery thrombosis, the only option is retransplantation.

Early portal vein thrombosis occurs usually within the first week (median, 2 days) after transplantation and requires emergency thrombectomy in most cases. It occurs in 5–10 % of recipients. It is more frequent in children transplanted for biliary atresia, because of pre-existing portal vein hypoplasia. Refractory ascites may indicate a portal thrombosis or stenosis of suprahepatic veins.

Biliary Complications

Bile duct complications (bile leaks, stenosis, strictures) are usually a result of technical problems or of ischemic injury of the donor duct [47, 48]. Early leaks can be diagnosed by the appearance of bile in the drains. Many leaks resolve with decompression by transhepatic tube drainage. Surgical revision of the anastomosis should be performed for those patients with bile peritonitis and those with persistent leaks. As discussed earlier, bile complications resulting from bile duct ischemia secondary to early hepatic artery thrombosis generally require re-transplantation (Table 29.5). Biliary strictures can occur later, even years after transplant, with bile duct dilatation on ultrasound or recurrent cholangitis. They can be definitively diagnosed and treated with percutaneous transhepatic cholangiography with stenting and dilatation, but surgical revision may be necessary in some cases.

Medical Considerations

Infections

Infection is the most common source of morbidity and mortality following transplantation. Because of immunosuppression, patients are at risk of developing nosocomial and opportunistic infections. In addition, the patient's preoperative condition may be a risk factor for sepsis. For example, patients with acute liver failure are known to have defective innate immunity, as characterized by hypocomplementemia and phagocytosis alteration, and children with chronic cholestasis have increased risk for bacterial peritonitis and recurrent cholangitis.

Bacterial sepsis occurs in the immediate post-transplant period and is more frequently due to Gram-negative enteric organisms, *Enterococcus* spp. and *Staphylococcus* spp. Fungal sepsis (*Candida* spp., *Aspergillus* spp.) may occur in the early posttransplant period and hold an elevated mortality if severe infection occurs, making monitoring of colonization index and early treatment mandatory. Frequent postoperative prophylactic regimens include acyclovir, amphotericin B, a β-lactam antibiotic, and trimethoprim-sulfamethoxazole. Although viral and opportunistic infections may occur later after transplantation, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex and adenovirus can cause early infection that must be recognized. The risk of developing either EBV or CMV infection is influenced by the preoperative serological status of the transplant donor and recipient. Seronegative recipients receiving seropositive donor organs are at greater risk. The development of effective methods of diagnosis, prophylaxis and treatment of CMV with gancyclovir or valgancyclovir means that these diseases are no longer a significant cause of mortality but morbidity remains high. In contrast, the absence of therapy for EBV means that infection rates are high. The development of molecular genetic diagnosis using polymerase chain reaction for EBV means that progressive disease, or post transplant lymphoproloferative disease (PTLD) may be prevented by preemptive reduction of immunosuppression in response to rinsing EBV titers. Various prophylactic protocols have been used to decrease the incidence of symptomatic CMV and EBV infection, although seroconversion in naive recipients inevitably occurs.

Acute Rejection

Despite improved immunosuppressive regimens, acute rejection remains a problem after liver transplantation, and about 20–50 % of patients develop at least one episode of acute rejection in the first weeks after liver transplantation [7, 49]. It can occur later, and is often associated with immunosuppressant noncompliance. The clinical picture includes fever, ascites, and jaundice. Rejection is generally suspected because of increasing liver enzymes and increase in gamma-glutamyltranspeptidase level. Liver biopsy is the key for

diagnosis, and histologic findings of acute rejection are a mixed portal inflammatory infiltrate, predominantly mononuclear cells associated with portal and central vein endothelitis and bile duct damage. The primary treatment is a short course of high-dose methylprednisolone, which is effective in treating rejection in 80 % of cases.

Other Complications and Re-transplantation

Early second look reoperation is commonly used in several centers for the best diagnosis and treatment of bile leakage, hemorrhage, bowel injury, and sepsis for instance. Digestive perforation occurs in 20 % of children with biliary atresia. Acute pancreatitis may occur in <2 % of children who undergo LT but is associated with high mortality. Postoperative cardiopulmonary failure is worth mentioning, as restrictive or obstructive cardiomyopathy (oxalosis, chronic cholestasis) and pulmonary hypertension (hepatopulmonary syndrome, pulmonary vein stenosis in Alagille syndrome) may be encountered.

Re-transplantation is not an uncommon event. Its overall incidence ranges from 10 to 20 % and occurs mainly within the first 30 days following initial transplantation [11, 50]. The majority of re-transplantation results from acute allograft a damage cause by either hepatic artery thrombosis or primary non-function, and acute graft rejection (Table 29.5).

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of diseases, ranging from benign lymphatic hyperplasia to lymphomas. It is favored by the intensity of the immunosuppression and the absence of prior exposure to EBV infection. Treatment of PTLD is based on the clinical aggressiveness of the syndrome and the immunological cell typing. In all cases documented PTLD requires an immediate decrease or withdrawal of immunosuppression. If the tumor expresses the B-cell marker CD20, the anti-CD20 monoclonal antibody rituximab are indicated.

In general recurrence of the primary liver disease in the graft is uncommon in children since liver diseases requiring LT are usually congenital biliary atresia and therefore LT is curative. However, a recurrence is possible if the LT indication is a primary sclerosing cholangitis. De novo autoimmune hepatitis can occur in any graft, regardless of the original disease, and is therefore not considered recurrence of the disease, but a new entity [51, 52]. It may be associated with the use of steroid-free regimes and occur in 2–3 % of children. This form of graft dysfunction is associated with an increasing incidence of non-specific antibodies (ANA, SMA, and rarely LKM), graft hepatitis and elevated immunoglobulins and may be related to the progressive development of graft hepatitis with fibrosis.

Chronic hepatitis has been recently recognized as a prevalent problem in late allografts [1, 53]. Liver biopsy shows a portal inflammation. The treatment of this condition is not clear.

Immunosuppression

The immune system recognizes the liver graft as "non-self" and begins a destructive immune response mediated principally by the T lymphocytes, especially the CD4+ T cell. In addition interleukin -2 (IL-2) activates the secretion of cytotoxic T cells, B cells and macrophages. In order to avoid destruction of the liver graft, immunosuppressive drugs must be administered. The immunosuppressive agents must interrupt the activation of CD4+ T cells and IL-2 production. The incidence of acute and chronic rejection has fallen following the development of newer immunosuppressive drugs, which are more easily absorbed such as cyclosporine microemulsion or more potent such as tarcolimus. The following are the main immunsuppressive drugs used in pediatric LT.

Corticosteroids

Corticosteroids are effective in both the prevention and the treatment of graft rejection. Their mechanisms of action are unclear, but they inhibit IL-2 and reduce the proliferation of T cells (helper and suppressor T cells, cytotoxic T cells), and the migration and activity of neutrophils. However corticosteroids have important side effects. Their use is associated with increased incidence of bacterial, viral and fungal infections, increased risk for developing malignancies, and detrimental metabolic effects in children. The most common metabolic side effects include bone marrow suppression, hypertension, diabetes mellitus, increased appetite, obesity, gastric ulcers, sodium and water retention. Long-term use may result in osteoporosis, growth retardation, avascular necrosis of joints, and depression. For these reasons, most pediatric centers have currently adopted steroid-free immunosuppressive protocols, combining calcineurin inhibitors and antibody to the IL-2 receptors of T cells (basiliximab).

Calcineurin Inhibitors

Progress in liver transplantation in the last 20 years has been characterized in large part by the introduction of calcineurin inhibitors, cyclosporine and tacrolimus, that today represent the keystone of most immunosuppressive protocols. These drugs inhibit T-cell responses and bind to intracellular proteins called immunophilins. This complex binds to and inhibits the phosphatase activity of calcineurin, which block the transcription of cytokines, particularly IL-2. The use of calcineurin inhibitors is associated with side effects, which include nephrotoxicity, neurotoxicity, and hypertension. Most of them are reversible after dose reduction or discontinuation of the drug.

The introduction of cyclosporine in the 1980s was a major advancement because it led to significant increases in patients' and graft survival rates, and a reduction in the incidence and severity of rejection. Administration of cyclosporine usually begins intravenously, during or after LT, with maintenance doses delivered orally. Absorption is dependent upon the presence of bile. Therefore, hepatic dysfunction might limit the absorption of cyclosporine. Microemulsions of cyclosporine are more easily absorbed and allow more stability in the of the desired blood concentration. However, many drugs interact with cyclosporine. Therefore, serum drug levels should be monitored closely. Cyclosporine is also associated with cosmetic side effects such as hypertrichosis and gingival hyperplasia. For all these reasons, over the last 10 years, the use of tacrolimus has increased, and nowadays it is preferred to cyclosporine.

Tacrolimus is 100 times more potent than cyclosporine. Moreover, tacrolimus is associated with less hyperlipidemia and a lower cardiovascular risk than cyclosporine. Comparison between tacrolimus and cyclosporine shows similar 1-year patient and graft survival, as well as steroid-resistant rejection in children treated with tacrolimus. Tacrolimus can be given as a 24-h continuous IV infusion or orally.

Daily determination of calcineurin inhibitors blood level is essential because it will help in dosing immunosuppressive therapy, and in balancing between the risk of infection (in case of over dosage) and rejection (in case of under dosage). Desired concentration of calcineurin inhibitors depends upon the time post – transplant. At 0–3 months post-transplant, cyclosporine and tacrolimus target levels are 200–250 mg/L and 10–15 mg/L, respectively. At 4–12 months post-transplant cyclosporine and tacrolimus levels should be at 150–200 mg/L and 8–10 mg/L, respectively. After 1 year the optimal levels are 50–10 mg/L for cyclosporine and 5–8 mg/l for tacrolimus.

IL-2 Receptor Antibodies

T cells involved in acute rejection act by exposing activation markers such as the IL-2 receptors. Anti IL-2 receptors (basiliximab) combined with anticalcineurin have drastically improved graft survival. Basiliximab is a chimeric (mouse and human) monoclonal antibody. Its safety and tolerability are excellent. As previously mentioned, the combination of these drugs allows steroid-free immunosuppression with no harmful effect on graft acceptance. The patient receives two doses of basiliximab, the first one should be given 6 h after organ reperfusion, and the second on day four after transplantation. This approach reduces hypertension, growth retardation, and the cosmetic effects of steroide therapy.

Other Immunosuppressive Drugs

Mycophenolate mofetil, a selective inhibitor of the inosine monophosphate deshydrogenase, has been successfully used as an alternative immunosuppressive agent in patients with chronic rejection, refractory rejection, or severe calcineurine inhibitor toxicity. Large inter-individual variations indicate the need for therapeutic drug monitoring and individualized dosing.

Sirolimus (rapamycin) is a macrolide antibiotic with immunouppressive properties that acts by blocking T-cell activation by way of IL-2R post receptor signal transduction. It has been used as rescue treatment in chronic rejection and calcineurin inhibitor toxicity.

Results and Outcome

Pediatric LT is one of the most successful solid organ transplants. Although the potential complications are numerous, the overall results of pediatric liver transplantation are excellent, especially for long-term outcome, as most indications for pediatric liver transplantation do not recur within the transplanted allograft, whereas disease recurrence represents a significant cause of long-term graft loss in adults.

Short-Term Results

Survival rates vary according to the age at transplantation and the underlying diagnosis. Survival for children less than 1 year old has improved dramatically [54]. The univariate predictors of graft loss are age less than 6 months, calculated creatinine clearance less than 90, pre-LT hospitalization, pre-LT mechanical ventilation, repeat LT, and infants transplanted for reasons other than cholestatic liver disease [54]. Neonates represent a special population and their outcomes from LT are worthy of consideration [27, 55, 56]. Although small babies have higher complication rates and longer hospital stays following transplantation, neonatal liver transplant recipients now have similar patient and graft survival compared with older children. The underlying diagnosis at transplantation also has an effect on outcomes. Patients with acute liver failure have worse early and long-term survival rates. Although the patient and graft survival are dependent on surgical techniques and patient care, their influence on survival is limited to the initial perioperative period and does not affect long-term outcome. Early postoperative death is mainly related to sepsis, graft failure, multiorgan failure, and cardiopulmonary and neurologic complications, whereas late mortality is mainly related to sepsis. From the SPLIT database, a total of 42 pre-, peri- and post-transplant variables were evaluated in

2982 pediatric recipients of a first LT [9]. Factors affecting patient and graft outcome at 6 months, reoperation for any cause increased the risk for both patient and graft loss by 11 fold and reoperation exclusive of specific complications by fourfold. Vascular thrombosis, bowel perforation, septicemia, and retransplantation, each independently increased the risk of patient and graft loss by three to fourfold. The only baseline factor with similarly high relative risk for patient and graft loss was recipients in the intensive care unit intubated at transplant.

Outcome, Long-Term Complications and Quality of Life

Overall survival of children after liver transplantation is 70–80 % in the largest series, and 15-year graft survival is between 52 and 65 % (Table 29.1). As techniques and patient care improve, actual survival can currently exceed 85 % [4]. Ten years after transplant, 79 % of children attend normal school and in 69 % of them school performance is not delayed [6]. Clinical factors associated with improved post-LT health-related quality of life 20 years after LT are younger age at LT allograft longevity, and strong social support. In a recent study, more than 90 % of pediatric survivors completed high school. After LT, 34 % of pediatric recipients married, and 79 % remained married at 20 years' follow-up [13]. Effective transition strategies from childhood to adulthood are important in adolescents since nonadherence to the treatment is common [57, 58]. One study has reported the psychological adjustment of 116 pediatric LT recipients reaching adulthood. In this study, 76 % considered their quality of life as good or very good. Poor compliance with medications was reported by 45 % of them. Anxiety, loneliness and negative thoughts were expressed by 53, 84, and 47 % of the patients, respectively. Among them, 11 % were being cared for by psychologists or psychiatrists [5].

Despite these encouraging results, late complications are possible. Seventy-three per cent of long-term survivors have abnormal liver histology with centrolobular fibrosis mainly due to chronic rejection [6]. Resistant linear growth impairment is also common in pediatric liver transplant population [59]. Renal dysfunction has also been noted in more than 30 % of long-term survivors [60]. This has modified immunosuppressive practices in at-risk transplant recipients. However current immunosuppressive agents are also associated with an increased risk for diabetes, dyslipidemia, and obesity [61–63]. Lifestyle modification and minimization of immune suppressants can be effective in reducing these risks. In summary, liver transplantation gives children with a potentially lethal disease an excellent long-term prognosis and quality of life.

Conclusions and Future Directions

Long-term outcomes for infants and children undergoing LT are excellent and have improved over time. The history of pediatric LT has clearly shown that success is dependant on constant collaboration between pediatricians, hepatologists, surgeons, nurses, transplant coordinators, dieticians, psychologists and social workers. The incidence of acute and chronic rejection has fallen following the development of newer immunosuppressive drugs and protocols. One major problem remains the lack of donors. In the U.S. the total number of pediatric liver donor has decreased in 10 years from 20 to 12 % [64]. Donation after cardiac death offers a new possibility to increase the pool of potential donors [40, 65]. In children with acute liver failure, increasing interest has centred on the possibility of providing temporary liver support based on extracorporeal devices (artificial and bioartificial) or on hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it. Similarly, hepatocyte transplantation offers new perspective in infants and children with metabolic failure. As long-term survival increases, attention has now focused on the quality of life achieved by children undergoing transplantation [5, 13, 57, 66].

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Intestinal/Multivisceral Transplantation

30

Gwenn E. McLaughlin and Tomoaki Kato

Abstract

Intestinal/multivisceral transplantation has evolved from an experimental procedure to the treatment of choice for patients with irreversible intestinal failure and serious complications related to long-term parenteral nutrition. Children who are likely to suffer permanent intestinal failure and benefit from intestinal transplantation include those with a remaining small bowel length of less than 30–40 cm, absence of the ileocecal valve, colonic resection and malabsorptive syndromes. Indications for transplant include frequent severe bouts of catheter associated sepsis, threatened loss of vascular access and the development of liver cirrhosis from cholestasis. Children who are more likely to experience cholestasis from total parenteral nutrition include those who experience persistent hyperbilirubinemia (greater than 6 mg/dl despite enteral nutrition), those with recurrent sepsis and/or bacterial overgrowth and those with minimal tolerance of any enteral feeds in the first few months post resection. The 1 year survival rate after intestinal transplantation has markedly improved over the last several years but long term survival rates have remained unchanged. The improved short term survival rates have led to an increased prevalence of this patient population in intensive care units. Management of intestinal and multivisceral transplant recipients is uniquely challenging because of complications arising from the high incidence of transplant rejection and its treatment. In the ICU, the complexity of medical care for the transplant recipient requires a multidisciplinary approach with coordination by an intensivist in collaboration with the transplant surgeon, gastroenterologist, and other specialists.

Keywords

Gastroschisis • Necrotizing enterocolitis • Multivisceral transplantation • Acute cellular rejection • Antibody mediated rejection • Chronic rejection • Graft vs. host disease • Calcineurin inhibitors • Tacrolimus • Thymoglobulin • Rituximab • Post-transplant lymphoproliferative disorder • Posterior reversible encephalopathy • Herpes virus infections • Viral infection, reactivation

Introduction

Intestinal/multivisceral transplantation has evolved from an experimental procedure to the treatment of choice for patients with irreversible intestinal failure and serious complications related to long-term parenteral nutrition. Each year nearly 200 individuals undergo intestinal transplantation and approximately one half of recipients are less than 18 years of age [1]. At the end of 2007, there were nearly 400 living

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pediatric intestinal transplant recipients [1]. Management of intestinal and multivisceral transplant recipients is uniquely challenging because of complications arising from the high incidence of graft rejection and its treatment. When performed in a young, immunologically naive population the likelihood of post-transplant life threatening infections is high. Long-term co-morbidities, such as diabetes, hypertension, chronic kidney failure, and neurological sequelae, also develop in this patient population, especially as short-term survival improves. Thus, the medical care of intestinal transplant recipients may involve the management of insufficiency of every organ system.

In the ICU, the complexity of medical care for the transplant recipient requires a multidisciplinary approach with coordination by an intensivist in collaboration with the transplant surgeon, gastroenterologist, and other specialists [2]. The majority of children are transplanted in a few high volume centers and increasing collective experience has contributed to improved survival [3]. When these patients present to ICUs distant from the home transplant center, early communication with that center is essential and transfer after stabilization may be necessary.

Indications for Transplant

Intestinal transplantation does not offer benefit for all children dependent on total parenteral nutrition (TPN). With new approaches to nutritional support and bowel lengthening procedures, 1 and 5 years survival rates for children with short bowel syndrome are 94 and 80 %, respectively [4]. Eighty percent of children can wean from TPN – most do so between 1 and 2 years of age [4]. Less than 10 % die from TPN related complications [4]. Whereas children were once institutionalized while receiving TPN, today many of these children can live at home while undergoing bowel rehabilitation.

Several reviews have identified the following characteristics of children who are likely to suffer permanent intestinal failure: remaining small bowel length less than 30–40 cm, absence of the ileocecal valve, and colonic resection [4, 5]. Children who are more likely to experience TPN-induced cholestasis include those who experience persistent hyperbilirubinemia (greater than 6 mg/dL despite enteral nutrition), those with recurrent sepsis and/or bacterial overgrowth, and those with minimal tolerance of any enteral feeds in the first few months post resection [4, 5]. Indications for transplant include frequent severe bouts of catheter-associated sepsis and threatened loss of vascular access [4]. Children should be referred for transplant evaluation when they experience liver fibrosis, a sustained bilirubin elevation over 5 mg/dL, signs of portal hypertension, and loss of 50 % of vascular access sites. A ratio of aspartate aminotransferase (AST) to platelet count greater than 1.5 was associated with the early development of fibrosis and may be used to guide the timing of listing for isolated intestinal transplantation [6]. Children with malabsorptive conditions such as micro-villous inclusion disease, tufting enteropathy and mega-cystic microcolon intestinal hypo-peristalsis syndrome should also be referred to a transplantation center as they have no intestinal rehabilitation potential [4, 5]. Waiting times for an isolated intestine allograft are much shorter than waiting times for a liver allograft [3]. Children who are ill enough to require hospitalization at the time of transplantation have a higher mortality than those waiting at home. Over the last several years short term survival rates have improved and fewer children are noted to be in the hospital at the time of transplantation, likely due to earlier referral [1].

Intestinal transplantation can also be used for the treatment of specific neoplastic diseases involving the mesenteric root. In pediatrics, neoplastic disease is an indication for transplant in approximately 1 % of cases. Moon et al. described a series of 15 patients, 12 of whom had desmoid tumors, who underwent multivisceral transplantation. This subset of patients had 1 and 5 years survival rates of 69 and 50 % respectively [7].

Pre-transplant Evaluation

The pre-transplant evaluation process is designed to identify contraindications to transplant and co-morbidities that will complicate the post-transplant course. Contraindications include profound neurologic deficits, non-correctable life-threatening conditions that are not related to liver and intestinal failure, immunodeficiencies, non-resectable malignancies, multisystem autoimmune disorders, and insufficient vascular access [4]. Cancer survivors must be 5 years out from their last treatment and cleared by an oncologist before being considered transplant candidates. Co-morbidities are common in intestinal transplant candidates. At the University of Miami, the most common cause of intestinal failure for pediatric intestinal transplant is gastroschisis (27 %) followed by necrotizing enterocolitis (20 %) [8]. These specific conditions are associated with prematurity, prolonged hospitalization, colonization with resistant pathogens, chronic lung disease, failure to thrive, poor vascular access, limited abdominal capacity, and poor nutrition. In adult transplantation, mesenteric thrombosis is a common primary diagnosis and a coexisting hypercoaguable state may lead to additional complications [8, 9].

A thorough history must include screening of the family history for thrombophilia, hypercholesterolism, and adverse anesthetic incidents. A thorough psychosocial evaluation is necessary to evaluate potential barriers to both emergency care and routine monitoring. Imaging including abdominal, central nervous systems and vascular access must be

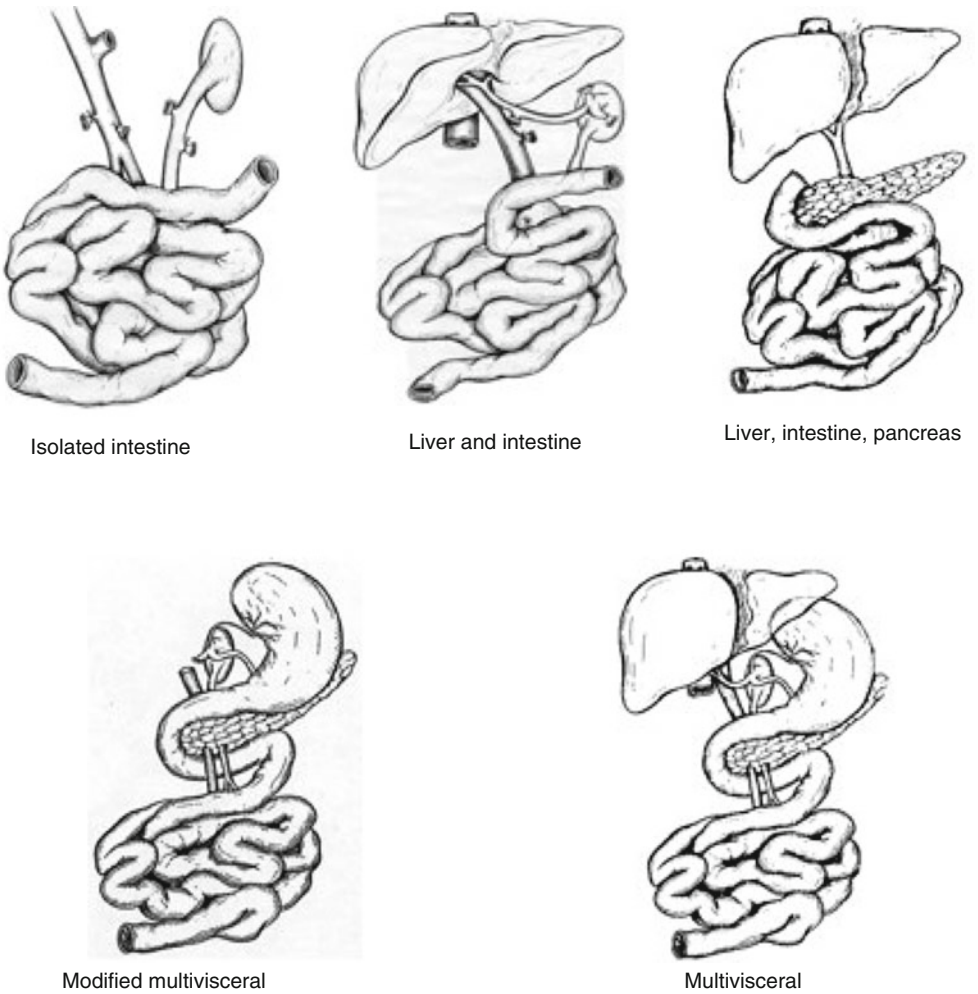

Fig. 30.1 Overview of types of grafts used in intestinal and multivisceral transplantation (Reprinted from Hopfner et al. [152]. With permission from SAGE Publications, Inc.)

reviewed. Certainly liver assessment is critical and liver biopsy to evaluate the extent of fibrosis is routine. Renal function should be evaluated to determine if a kidney should be included in the graft. Serologic tests for HIV, hepatitis B and C are required. Every effort is made to bring the child into compliance with vaccination recommendations before transplant. The complete pre-transplant evaluation should be available to the intensivist. Ideally, a pediatric intensivist should participate in a meeting where candidate eligibility is discussed prior to listing.

Surgical Approach

There are several surgical approaches to intestinal transplantation [8]. Figure 30.1 gives an overview of the different types of grafts used in intestinal transplantation. Isolated intestinal transplantation has an advantage over combined transplants in that the intestine can be explanted should severe rejection or other complications such as posttransplant lymphoproliferative disorder (PTLD) arise. With this scenario, the patient becomes TPN dependent once again and immunosuppression is stopped. If the child has significant hepatic fibrosis or liver dysfunction and a liver transplant is required, it is recommended that the transplantation of the liver is performed at the time of intestinal transplantation. A combined liver and intestinal transplant may include the duodenum and pancreas, whole or in part, for technical reasons [2]. The term *multivisceral transplantation* applies to the en bloc replacement of liver, pancreas, stomach, and small intestine after evisceration of native abdominal organs including the spleen; however, there is great variability in the extent of transplantation of other organs such as the spleen and proximal colon [2, 3, 8, 10]. Colonic transplantation was once thought to be associated with higher infection rates, but this appears to no longer be true and colonic transplantation may reduce fluid losses [8, 11, 12]. A *modified multivisceral transplantation* refers to en bloc transplantation of multiple abdominal organs excluding the liver [8, 9]. To simplify clinical research, some scientists have recommended that procedures be categorized as intestinal transplant with or without liver transplant and the term multivisceral be abandoned [3].

However, these terms are already recognized and used in comparative analysis of specific transplant type [10].

Postsurgical Care and Surgical Complications

Upon reperfusion the transplanted intestine undergoes significant swelling. The patient requires aggressive fluid resuscitation and the edema may prevent closure of the abdomen. Postoperatively, central venous pressure (CVP) monitoring and close attention to perfusion, abdominal fluid losses, and urine output is crucial. In small children, the preoperative blood pressure may be the best guide for postoperative target blood pressure to prevent excessive fluid overload. Hypotension not responsive to fluid administration is relatively rare, and there is no data to support the use of a specific vasoconstrictor for hypotension at this time [2]. In fact, hypertension is more frequent than hypotension in these patients related to corticosteroids, IV calcineurin inhibitors, and hypervolemia. Hypertension is typically managed by short-acting calcium channel blockers [2]. Frequent assessment of serum lactic acid concentrations can also guide fluid therapy. Oncotic pressure is often low as evidenced by hypoalbuminemia, and albumin supplementation may be beneficial. The large aortic anastomosis reduces the risk of hepatic artery thrombosis seen in isolated liver transplantation. Still, there are concerns about intestinal perfusion. Therefore, the hemoglobin is maintained at around 9–10 mg/dl and mild abnormalities of coagulation are not corrected [2]. Platelet counts are typically as low as 40,000 without evidence of bleeding and are not corrected. The color of the stoma must be frequently observed. When combined with a small abdominal compartment, abdominal distension may compromise diaphragmatic excursion and functional residual capacity. If there is any question of intra-abdominal hypertension, bladder pressure should be measured [2].

Typically capillary leak begins to subside 24 h postoperatively. At this time IV fluids can be gradually decreased. Postoperative ileus generally persists for several days, so continuous gastric suctioning is necessary to reduce intraluminal pressure. Most centers begin feeding around the fifth postoperative day upon detection of bowel sounds and stoma output but a few wait until 10–14 days postoperatively [13]. Short peptide-based isotonic formulas are infused at small but increasing volumes, while optimal intake is supported by parenteral nutrition [13]. Due to lymphatic disruption, absorption of fat as chylomicrons is impaired until collateral channels reform at around 180 days postoperatively [13]. Some centers supplement with intralipids or medium chain triglycerides and fat soluble vitamins [13]. It is not unusual to have high ostomy output. This can be controlled with anti-peristaltic agents such as loperamide and diphenoxylate in high doses.

There are few reports of the surgical complications after transplantation. Intestinal perforation/anastomotic leak appears to be the most common complication, followed by sub-acute bowel obstruction, often related to ostomy prolapse [14]. Intestinal perforation can be difficult to detect as the use of steroids diminishes an inflammatory response and the typical signs and symptoms of rebound tenderness and fever may be lacking [2]. The incidence of abdominal compartment syndrome has been reduced by staged closure of the abdomen [15]. Other complications include portocaval thrombosis, biliary leak, wound dehiscence, intra-abdominal bleeding, failed abdominal closure, and fistula formation [2, 14]. Rarely, mycotic aneurysm at the aortic anastomosis can occur due to a relatively high level of contamination of the surgical field. Aneurysm rupture leads to a sudden catastrophic intra-abdominal bleeding. Frequent monitoring and use of imaging studies such as ultrasound and CT can assist the clinician in identifying fluid collections and thrombotic complications [2].

Complications Related to Immunosuppression

Immunosuppression Protocols

The first attempts at intestinal transplantation over two decades ago often failed due to refractory acute rejection and its common sequelae, bacterial infection [15]. With the introduction of tacrolimus-based immunosuppression in 1990, the short-term survival of intestinal transplant recipients has substantially improved, but long-term patient survival remains challenging [1, 3]. Intestinal and multivisceral transplants differ from other solid organ transplants because of the complex interaction between the intestinal allograft and the native immune system, including the gut-associated lymphoid tissue (GALT) of the bowel mucosa [16]. There is evidence that enterocytes have the capacity to function as antigen presenting cells resulting in stimulation of donor lymphocytes [17]. As a consequence, intestinal and multivisceral transplant recipients need greater immunosuppression than other solid organ recipients and experience higher rates of acute and chronic rejection [1].

The implementation of efficient induction therapy reduces the risk of rejection [8, 9, 11, 16, 18–21]. Induction therapy varies by center but typically consists of anti-lymphocyte preparations such as rabbit anti-thymocyte globulin (rATG, Thymoglobulin®, Genzyme, Cambridge, MA), alemtuzumab (Campath-1H®, Berlex Laboratories, Montville, NJ) or daclizumab (Zenapax®, Roche Pharmaceuticals, Nutley, NJ) [1, 3, 8, 9, 11]. However, the use of Campath-1H in pediatric transplant recipients was associated with significantly higher morbidity and mortality due to infection in children younger than 4 years [21]. Maintenance immunosuppression consists of the calcineurin inhibitor tacrolimus (Prograf®, Fujisawa

Pharmaceuticals, Deerfield, IL) and steroids. The initial tacrolimus target whole blood trough concentration measured at 12 h also varies by center but is generally over 10 ng/mL for the first 3 months. Subsequently, concentrations are kept slightly lower, 8–12 ng/mL [1–3, 8, 9]. High dose steroids are given intraoperatively (up to 50 mg/kg) and tapered over the first 4 days. Maintenance steroid management also varies by center, some reduce the steroid dose 2–4 weeks after transplant, and others reduce the steroid dose 6–9 months after transplantation [1]. Whether specific induction therapies will permit reductions in long term immunosuppression and improve long term survival in intestinal and multivisceral transplants recipients is still being evaluated.

Acute Cellular Rejection

Acute cellular rejection (ACR) occurs in approximately 40 % of children after intestinal transplantation, generally within the first 3 months post-transplant [1, 21, 22]. In multivisceral transplantation, the most common site of ACR is the intestine, while other organs appear to be spared [8]. Although non-compliance is a risk factor for transplant rejection, documentation of non-compliance is difficult in intestinal transplantation. Tacrolimus is metabolized by enterocytes and impaired metabolism during rejection results in elevated tacrolimus concentrations at the time of presentation with rejection [23, 24]. Acute cellular rejection is characterized by fever, diarrhea, abdominal pain and/or distension, and is often associated with positive blood cultures due to bacterial translocation of enteric organisms [25]. For this reason, some authors recommend initiation of prophylactic anti-bacterial and anti-viral therapy during any episode of intestinal allograft rejection [26]. The systemic inflammatory response that accompanies rejection can mimic sepsis with fever, tachycardia, tachypnea, hypoxemia, metabolic acidosis and hypotension, and requires careful monitoring and aggressive resuscitation.

Early detection of rejection is crucial as ACR remains the greatest risk factor for permanent graft failure; especially, if there is a severe rejection episode or if rejection is not resolved within 21 days [8, 21]. Surveillance endoscopic biopsies and zoom video endoscopy are currently performed biweekly during the first month, weekly during the next 2 months, then monthly afterward. Intestinal rejection can be localized: therefore, multiple biopsies must be obtained from several locations. Additional endoscopies are required when fever, diarrhea, or bacteremia occur. During suspected or proven episodes of rejection, endoscopies are performed as often as every other day until symptoms and the histopathological features resolve [22].

The endoscopic findings of ACR include blunted villi, edematous and friable mucosa, ulcers, and mucosal exfoliation [27]. Histopathologically, acute allograft rejection is graded mild (grade 1), moderate (grade 2) or severe (grade 3) based on a combination of crypt injury, mucosal infiltration primarily by mononuclear cells, and increased crypt cell apoptosis (Fig. 30.2) [27]. Exfoliative severe rejection is defined by denudation of the intestinal epithelium and is associated with high rates of mortality and graft loss [28].

Acute cellular rejection is treated by modulation of immunosuppression (Table 30.1). Mild acute rejection is treated with pulsed steroids (methylprednisolone 15–30 mg/kg), followed by a weaning cycle along with an increase in targeted tacrolimus concentration to early post-transplant values. Steroid-resistant episodes as well as moderate and severe rejection are generally treated with Muromonab-CD3 (Orthoclone OKT3®) or Thymoglobulin [1, 21]. Treatment can vary from a single dose to 14 days of therapy depending on severity and response [1]. In a recent adult series, four cases of OKT3 resistant and three cases of steroid resistant ACR responded to infliximab, a monoclonal antibody which blocks TNF α (alpha) [29].

Since histopathologic changes are a delayed manifestation of rejection and may occur in isolated areas, potential biomarkers for accurate early detection of rejection have been investigated. Plasma citrulline, synthesized exclusively by enterocytes of the small intestine, has been used as a biomarker of intestinal mass and function in patients with intestinal failure [30, 31]. Several recent studies have shown a strong correlation between lower plasma citrulline concentrations and grade of rejection [32–34]. Using a citrulline concentration cutoff point of 13 μmol/L for moderate or severe ACR, the sensitivity was 96 %, but specificity was only 69 %. A plasma citrulline concentration of more than 13 μmol/L excluded moderate and severe ACR with greater than 99 % certainty [33]. Because normal plasma concentrations of citrulline take up to 3 months to achieve after intestinal transplant, this assay is not useful in the first weeks post-transplant [34]. Moreover, plasma citrulline concentrations decrease only after epithelial destruction, which makes it less useful as an early marker of rejection.

Fecal calprotectin, produced by neutrophils and macrophages, is elevated in conditions with mucosal leukocyte infiltrate such as inflammatory bowel disease, and has been evaluated as a screening tool to indicate a need for endoscopy, but does not seem to be able to differentiate between ACR and other intestinal pathologies [35–37]. In addition to biomarkers of rejection, direct measures of immune system activity such as complement-dependent cytotoxicity panel-reactive antibody testing (CDC-PRA), peripheral lymphocyte subsets and the ImmuKnow® (Cylex Inc., Columbia, Maryland, USA) immune cell function assay are under investigation as early indicators of rejection risk or excessive immunosuppression [38, 39].

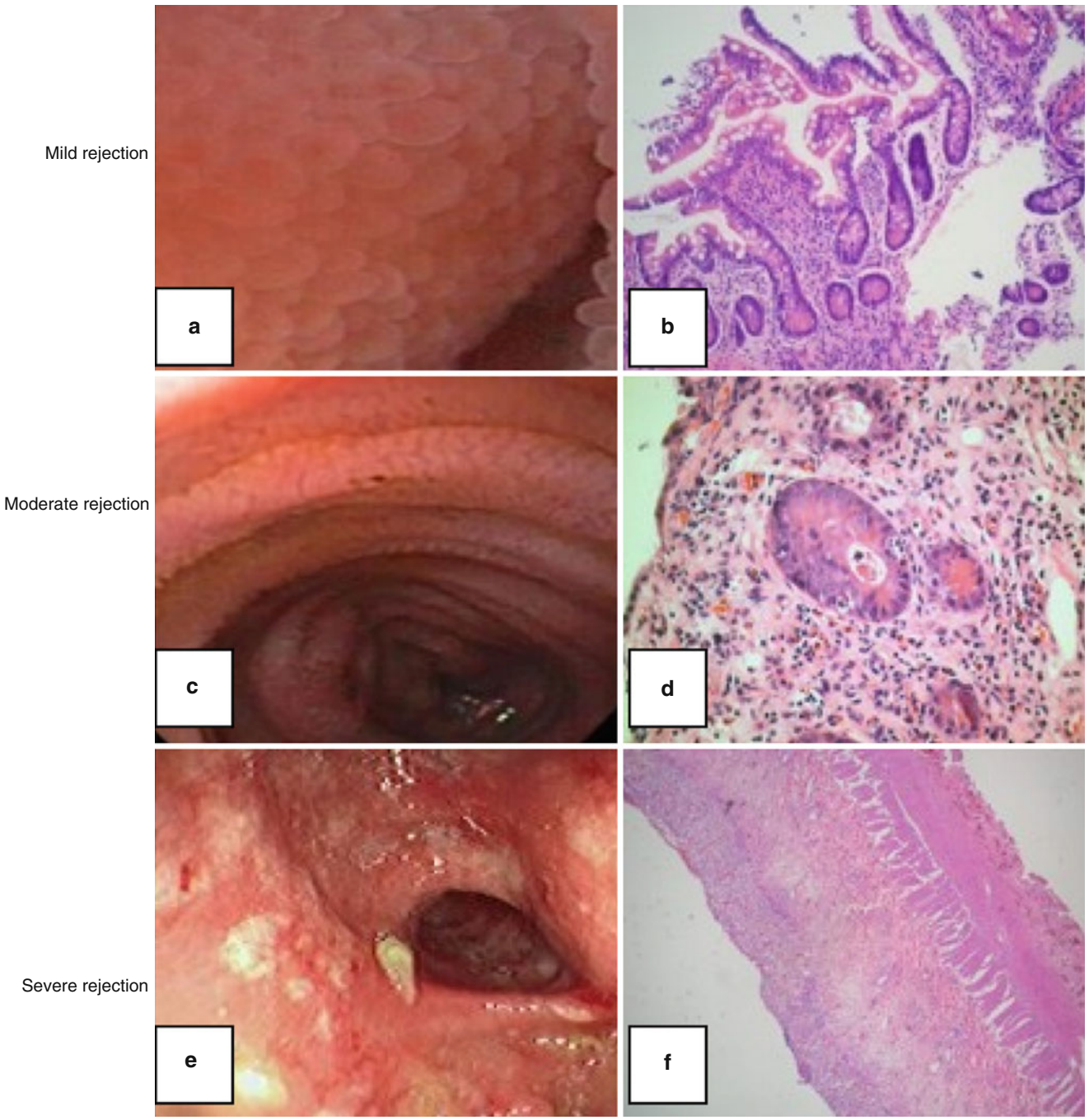

Fig. 30.2 Endoscopic findings and histopathology of acute cellular rejection (*ACR*): Mild ACR (grade 1): Mild mixed inflammatory infiltrate in lamina propria. Few apoptotic bodies in crypts (**a**, **b**). Moderate ACR (grade 2): Increase of mixed inflammatory infiltrate in lamina propria with frequent apoptotic bodies in crypts and confluent apoptosis (**c**, **d**). Severe ACR: (grade 3). Marked degree of crypt damage and architectural distortion with loss of crypts. Marked diffuse mixed inflammatory infiltrate with epithelial cell apoptosis in the surviving crypts (**e**, **f**) (Reprinted from Hopfner et al. [152]. With permission from SAGE Publications, Inc.)

Table 30.1 Overview of treatment of acute cellular rejection dependent on severity

Severity of rejection	Treatment	Rescue treatment
Mild rejection	Steroid bolus and cycle	Consider Thymoglobulin
	Increase in baseline immunosuppression	
Moderate rejection	Muromonab-CD3 (Orthoclone OKT3®) or Thymoglobulin (1–14 days)	
	Increase in baseline immunosuppression	
Severe rejection	Muromonab-CD3 (Orthoclone OKT3®) or Thymoglobulin (14 days)	Consider removal of graft for treatment failures
	Increase in baseline immunosuppression	

Antibody Mediated Rejection

Circulating donor specific antibodies have long been known to be associated with hyperacute rejection where organ dysfunction develops in minutes to hours after transplant due to pre-existing antibodies to donor tissue that bind to endothelium and activate complement [40]. Plasmapheresis combined with intensified immunosuppression has shown some success in single organ transplant recipients. High dose immunoglobulin (IVIG) has also been associated with decreased antibody titers and successful reversal of humoral rejection [40]. While plasmapheresis and IVIG reduce circulating antibodies, Rituximab, a monoclonal antibody against CD20 present on B-lymphocytes, has been used to stop antibody production [41, 42]. Acute humoral rejection is not specifically reported in intestinal transplant but may play a role in a few patients with early decompensation.

Antibody–mediated rejection is increasingly considered to play a role in delayed graft rejection, ACR not responsive to immunosuppression, and in chronic graft rejection. Approximately 20 % solid organ transplant recipients develop donor specific antibodies to HLA class I or II donor antigens, non-HLA antibodies to blood group antigens, and endothelial antigens [40]. Circulating antibodies are not always associated with organ dysfunction, but patients with HLA antibodies have significantly higher rates of graft failure [40]. Kato and colleagues showed HLA antibodies developed in 5 of 28 patients post intestinal/multivisceral transplantation [43]. Three of the five patients had strongly positive plasma reactive antibody (PRA) titer; all three had temporally associated significant episodes of acute rejection; whereas only 1 of the 25 patients with a weak or negative PRA titer had a rejection episode around the time of sampling [43]. Other investigators reported correlation between humoral sensitization and vascular changes in the intestinal mucosa [44].

Chronic rejection is one of the most common causes of intestinal graft loss in the second post-transplant year [8]. In a recent retrospective study, chronic rejection was diagnosed in approximately 20 % of isolated intestinal transplants and 5 % of multivisceral transplants [45]. The reason for the lower incidence of rejection in the latter group is unclear. Some investigators hypothesize that it is due to the protective effect of the liver or the preceding evisceration and thus decreased recipient lymphocyte population. Patients typically present with abdominal pain, chronic diarrhea, and weight loss. Major histological features of chronic rejection are nonspecific and include progressive obliterative arteriopathy, apoptosis, mural fibrosis and perivascular inflammation. In multivisceral transplants, the pancreas might be the organ most susceptible to chronic rejection [45]. Currently, re-transplantation is the only definitive treatment for chronic rejection with graft failure [46], but if chronic rejection is an antibody mediated process there are potential new therapeutic approaches [40]. Bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma, causes apoptosis in plasma cells, thereby decreasing alloantibody production. It has been found to be useful in treating antibody mediated rejection in kidney transplant recipients and may become a promising agent in the treatment of rejection after intestinal and multivisceral transplantation [47]. A recent case report showed successful reversal of refractory rejection with bortezomib in a patient following multivisceral transplantation [48]. Similarly, blockade of terminal complement activation by eculizumab, a humanized monoclonal antibody with high affinity for C5, appeared effective in a case report of ACR in a kidney transplant recipient [49].

Graft-Versus-Host Disease

Graft-versus-Host Disease (GvHD), defined as a reaction of donor immunocompetent cells against host tissue, occurs in 4–10 % of intestinal transplant recipients [8, 21, 50]. In classic GvHD seen after hematopoietic stem cell transplantation, inflammatory cytokines and donor derived lymphocytes damage skin, native liver and native intestine. In intestinal/multivisceral organ transplantation, however, the skin is often the only involved organ, although pulmonary GvHD is reported [50]. The diagnosis is based on clinical symptoms, detection of mixed chimerism with circulating donor lymphocytes, and histopathology. In a retrospective analysis of 46 children undergoing intestinal/multivisceral transplantation, five patients developed GvHD at a median time of 47 days after transplantation [50]. All of the patients had

cutaneous symptoms with a maculopapular generalized rash, and two patients had native gastrointestinal involvement in the form of diarrhea. In addition, three patients developed respiratory symptoms and four patients had severe hematologic abnormalities (pancytopenia, T-cell lymphoma, myeloid dysplasia, autoimmune hemolytic anemia). Three of the five patients with GvHD died a few months after diagnosis. In another study of 123 children, six developed confirmed GvHD, (0.5 ± 0.1 cases per 100 patient months of follow-up), and four of these six died [8]. The risk of GVHD appears to be greater in multivisceral transplantation than in isolated intestinal transplantation [8].

Although there is no proven standard therapy for GvHD, the initial approach is reduction of the maintenance immunosuppression and high dose steroids. The prognosis worsens dramatically for steroid-nonresponders [51, 52]. Salvage regimens include sirolimus, mycophenolate-mofetil and pentostatin, a nucleoside analog that irreversibly inhibits adenosine deaminase resulting in severe immunosuppression [53]. In addition, various monoclonal antibodies and anti-cytokine therapies such as infliximab/etanercept (anti-TNF α (alpha)) and daclizumab (anti-IL2 receptor) have been evaluated and show success in the treatment of GvHD in patients after bone marrow transplant [53–55]. In steroid resistant multivisceral recipients with a transplanted spleen, splenectomy is a possible last resort treatment option [8]. Extracorporeal photochemotherapy (ECP) is a promising therapeutic procedure that is currently under examination in a prospective multicenter phase 3 trial [56, 57]. Extracorporeal photochemotherapy (ECP) kills T-cells by first exposing them to the chemical methoxsalen and then ultraviolet A light [57].

Other Postoperative Complications

Infectious Complications

The main determinants of infectious complications in transplant recipients are the degree of immunosuppression and exposure to pathogens through the transplanted organ or the environment [58, 59]. A similar pattern of post-transplant infections has been described when institutions use similar tacrolimus or cyclosporine based immunosuppressive regimens following solid organ transplant; however, in the era of induction therapy for pediatric intestinal/multivisceral transplantation viral infections seem to appear earlier than previously reported in other transplant populations [38, 58, 59]. These viruses have a predilection for the graft and therefore may be activated latent infections from donor derived tissues [60]. Cytomegalovirus infection occurs in 30 % of recipients, while adenovirus is reported in 20 % of recipients [61–63]. The use of antiviral prophylactic strategies has made herpes virus infections uncommon, but the use of reverse transcriptase polymerase chain reaction (RT-PCR) assays for the detection and monitoring of viral DNA has identified other pathogens, including polyoma viruses such as BK virus and paramyxoviruses such as parainfluenza and metapneumovirus [38, 64]. Recurrent and chronic viral infections may eventually lead to graft dysfunction [45]. Opportunistic infections such as *Pneumocystis jiroveci* pneumonia and *Toxoplasma spp* can be prevented with trimethoprim-sulfamethoxazole (TMP/SMX).

Respiratory Failure

Intestinal/multivisceral transplant recipients observed over a 10 year period at the University of Miami were four times more likely than liver transplant recipients (24 % versus 6 %) to be re-admitted to the ICU with respiratory failure after transplantation [65]. The overall survival rate for intestinal/multivisceral transplant recipients who developed respiratory failure after transplant was 75 %, higher than the 58 % observed in a liver transplant population and higher than survival rates generally reported following bone marrow transplantation [8, 66–68]. This difference may be explained in part by the high prevalence of pulmonary edema from fluid overload and low oncotic pressure complicating acute tacrolimus toxicity in intestinal/multivisceral transplant recipients experiencing rejection. Less common non-infectious causes include transfusion related lung injury, GvHD, diffuse alveolar hemorrhage, and sirolimus toxicity [66–68]. Sirolimus-induced pneumonitis is reported in at least 2 % of liver transplant recipients and should be suspected in patients who develop respiratory symptoms while receiving sirolimus [68]. When intestinal and/or multi-visceral transplant are performed in children with a diminished abdominal cavity, abdominal distension can limit diaphragmatic excursion and compromise respiratory function.

Infectious pulmonary complications in intestinal/multivisceral transplant recipients include bacterial pneumonia, viral pneumonitis and acute respiratory distress syndrome (ARDS) related to sepsis. In one single center, pneumonia related respiratory failure occurred in 18 % of patients and was associated with younger age and higher mortality [8]. Due to a lack of published data on respiratory failure in intestinal transplant recipients, extrapolation of management principles from other immunocompromised populations is required. Optimal outcome depends on identifying the cause of the lung infiltrate through analysis of tracheal fluid, bronchoalveolar lavage fluid or tissue obtained from open lung biopsy and instituting specific therapy at the earliest possible time [67–69]. In a prospective cohort of 200 immunocompromised patients with infiltrates, infectious agents were recovered in over three fourths of all subjects [67]. While some viral infections such as influenza and RSV can be detected via immunoflourescence assay or culture from nasopharyn-

Table 30.2 Common viral pathogens isolated in transplanted children with lower respiratory tract infection

Rhinovirus
Influenza
Parainfluenza
Respiratory syncytial virus
Adenovirus
Metapneumovirus

geal washing samples, the detection of common respiratory viral pathogens has been improved by use of RT-PCR applied to nasopharyngeal and endotracheal samples [64, 70, 71]. Through this technology, community acquired viruses such as influenza virus, parainfluenza virus, adenovirus and rhinovirus have been increasingly recognized as major causes of serious lower respiratory illness in transplanted children (Table 30.2). Due to the diminished inflammatory response in immunocompromised patients typical radiologic appearance for any infectious agent may be absent [72]. In half of adults with neutropenia and in adult kidney transplant recipients computed tomography images revealed lesions not visualized on plain radiographs [71–74]. Studies have shown that in 70–86 % of mechanical ventilated patients, information obtained from open lung biopsy resulted in significant changes in management [75–77]. Because viral killing requires T-cell activation and therefore leads to severe pneumonia, immunosuppression needs to be profoundly reduced and even withheld for several days to allow immunologic recovery while increasing monitoring of the graft [2].

Respiratory failure in intestinal/multivisceral transplant recipients should be managed as it is in other critically ill populations with a few caveats. The use of non-invasive ventilation should be limited to a select population. Disrupted innervations of the transplanted stomach and/or proximal intestine impair gastrointestinal motility and increase the risk of aspiration. In addition, a small abdominal compartment may be compromised by intra-abdominal hypertension with even a small increase in intestinal air. Once intubated, sedation can be difficult in this population and higher doses of sedatives are required either because of upregulated drug clearance enzymes or a high liver mass to body weight ratio. Typically, when plateau pressures are greater than 30–35 cmH_2O we have implemented high frequency oscillatory ventilation. This requires pharmacologic paralysis in a population with many risk factors for prolonged paralysis and critical illness polyneuropathy so drug holidays and or daily monitoring of train of four are recommended.

Sepsis and Septic Shock

Bacterial sepsis is a major cause of mortality in organ recipients and early-onset bacteremia is associated with greater mortality compared to late-onset bacteremia after solid organ transplant [78]. Blood stream infection occurs more frequently in recipients of intestinal transplantation than in other types of solid organ transplantation [26]. This is mainly due to the presence of bacterial flora along the lumen of the allograft, enterocyte injury during rejection, the higher amount of immunosuppressive therapy, and the development of lymphoproliferative disorder [26, 79, 80]. Enteric bacteremia is an indication for endoscopic evaluation and biopsy of the graft to rule out rejection. As shown in multiple studies, early initiation of antibacterial therapy has had a direct effect on reducing mortality in sepsis and a transplant recipient should receive empiric antibiotics whenever febrile [81–83]. This includes coverage for enteric gram negative and gram positive organisms such as *Enterococcus spp*. Antifungal coverage may also be appropriate. Early goal-directed therapy requires intravenous access for fluid resuscitation and vasoactive therapy, ongoing patient assessment, and normalization of the physiologic parameters mean arterial pressure and mixed venous oxygen saturation; this approach results in a decrease in both in-hospital and overall mortality [84, 85]. A state of absolute or relative adrenal insufficiency has been well described in sepsis [85]. Transplant recipients are at greater risk due to long-term steroid use. Therefore, stress-doses of hydrocortisone with or without fludrocortisone should be administered. In the presence of active bacterial infections and no evidence of graft rejection, a reduction in immunosuppression is appropriate for transplant recipients but by how much and for how long is uncertain.

Acute Kidney Injury

Recipients of intestinal/multivisceral transplants have multiple risk factors for development of acute or chronic kidney failure, both pre- and post-transplant. Predictors of renal dysfunction include low pretransplant glomerular filtration rate (GFR), critical illness prior to transplant, and high-dose tacrolimus therapy [86]. At the time of transplant many recipients have already has a decline in GFR, on average to 83 % of the norm [86]. Although this renal dysfunction appears relatively mild, it predisposes to further decline of the kidney function after transplantation due to lower renal reserve. Post-transplant, recipients receive prolonged therapy with the nephrotoxic calcineurin inhibitors, tacrolimus or cyclosporine [87–89]. A higher incidence of infections mandates exposure to nephrotoxic antimicrobials. Other common complications post-transplantation also contribute to an increased risk of renal dysfunction, e.g. hypoperfusion, dehydration, chronic hypertension, diabetes mellitus, infection with BK virus and dyslipidemia.

The overall incidence of acute kidney injury (AKI) after adult solid organ transplantation is approximately 25 % with 8 % requiring renal replacement therapy [90]. In the intestinal/multivisceral transplant patients, acute tacrolimus toxicity is a common cause of AKI. This is in part due to an erratic intestinal absorption of tacrolimus and its metabolism by enterocytes. In the face of low renal reserve, whole blood tacrolimus concentrations over 20 ng/mL are associated with elevated serum creatinine, blood urea nitrogen (BUN), and oliguria [90]. Various vasoregulatory molecules, including endothelin and adenosine, are involved in calcineurin inhibitor related renal artery vasoconstriction [90]. Hence, acute tacrolimus toxicity frequently does not respond to diuretic therapy. Fenoldapam, a selective dopamine-1 receptor agonist that decreases vascular resistance while increasing renal blood flow, preserves renal function by counter-balancing the renal vasoconstrictive effects of cyclosporine in kidney and liver transplant patients [91, 92]. Aminophylline, a nonselective adenosine receptor antagonist, enhanced the response to loop diuretic in pediatric abdominal organ transplant recipients [93].

The indications for renal replacement therapy in multiple organ transplantation are the same as in other patient populations [94]. Peritoneal dialysis is not an option in the child after extensive abdominal surgery with removal of the peritoneum. Continuous venovenous hemodiafiltration is preferred to intermittent hemodialysis in many centers because of the latter's potential for large fluid shifts leading to hypotension and reduced organ perfusion [94]. Limited vascular access is a common finding in patients with intestinal failure, and functional vascular access is the most important technical component determining successful provision of continuous renal replacement therapy. In children less than 10 kg, circuit survival is significantly lower with smaller catheter size [95]. Furthermore, extracorporeal circuit volumes comprising more than 10–15 % of patient blood volume must be primed with whole blood to avoid hypotension and anemia, yet the bradykinin release syndrome (BRS) with acute hypotension is often associated with blood priming of the circuit [96]. Because multivisceral transplant patients are often poor candidates for hemodialysis, AKI must be prevented by close monitoring of tacrolimus concentrations and renal function, and avoidance of nephrotoxic drugs and hypoperfusion.

Chronic Kidney Disease

The incidence of chronic kidney disease (CKD) in adult intestinal and multivisceral transplant recipients 5 years after transplantation is 21.3 % and therefore higher than in other solid organ transplant populations [86]. Long-term use of calcineurin inhibitors is a major risk factor for the development of kidney dysfunction and the cumulative tacrolimus concentration has been described as predictor of decreased GFR, both in children and adults [8, 87, 97]. In a study of 44 pediatric intestinal transplant patients, without acute tacrolimus toxicity, the mean GFR decreased significantly from 138 mL/min/1.73 m [2] pre-transplantation to 102 mL/min/1.73 m [2] 18–24 months post-transplantation [97]. In rapid and persistent deterioration of the kidney function, sirolimus, a macrolide with potent immunosuppressive properties, can be used as maintenance therapy instead of tacrolimus. However, in intestinal organ transplants experience with sirolimus is limited. Several intestinal/multivisceral transplant recipients have undergone subsequent kidney transplants [1].

Hematologic Complications

After organ transplantation derangement of all hematopoietic cell lines has been described, resulting in anemia, leukocytopenia and thrombocytopenia. Generally cytopenia arises from decreased production or increased destruction of cell lines due to infection, drug toxicity, and formation of autoantibodies. Hematologic complications are best described after kidney, heart and liver transplantation. Several drugs used for immunomodulation, antiviral and antibacterial treatment or as ancillary therapy can cause hematologic side effects; in intestinal multivisceral transplantation, most importantly tacrolimus, mycophenolate mofetil, sirolimus, ganciclovir and TMP/SMX [98–100].

Post-transplant anemia is frequent after pediatric solid organ transplantation, affecting 85, 68 and 82 % of patients at 1 month, 12 months and 5 years, respectively [101]. The most common reason for anemia in transplant patients is iron deficiency secondary to poor nutritional iron supplementation and depletion of iron stores. In addition, in pediatric patients frequent phlebotomies after major surgery can play a significant role in the development of anemia [102]. Pure red cell aplasia (PRCA) or selective suppression of red cells is much less frequent than pancytopenia [101]. In vitro studies have shown no direct suppression of the bone marrow by tacrolimus, but reversible pure red cell aplasia has been reported [101, 103].

Neutropenia occurs in more than 10 % of transplanted patients related to drugs and infections [104]. Ganciclovir and valganciclovir, routinely used in intestinal and multivisceral transplant recipients for prophylaxis and treatment of CMV infection, are associated with neutropenia, as is TMP/SMX, used for prophylaxis of *Pneumocystis jiroveci* [105]. Bone marrow suppression associated with medication is usually reversible with dose reduction or discontinuation [106, 107]. Alternative options for prophylaxis in case of TMP/SMX toxicity are pentamidine and dapsone. In addition, treatment with hematopoietic growth factors (G-CSF, GM-CSF) can shorten the duration of drug-induced severe neutropenia and

Table 30.3 Drugs commonly used in transplant recipients incriminated in the occurrence of severe neutropenia and agranulocytosis

Drug category	Frequently used drugs in transplant recipients incriminated in neutropenia
Antimicrobials	Aciclovir, cephalosporins, ciprofloxacin, clindamycin, dapsone, fluconazole, ganciclovir, gentamicin, imipenem, linezolid, macrolides, metronidazole, penicillins, rifampicin, trimethoprim–sulfamethoxazole, valganciclovir, vancomycin
Anticonvulsants	Phenytoin, valproic acid
Cardiovascular drugs and diuretics	Acetazolamide, coumarins, hydralazine, metolazone, nifedipine, propranolol, spironolactone, thiazides, ticlopidine
Gastrointestinal drugs	Cimetidine, famotidine, metoclopramide, omeprazole, ranitidine
Immunomodulators	Alemtuzumab, infliximab, glucocorticoids, mycophenolate-mofetil, OKT3, rituximab, sirolimus, tacrolimus, thymoglobulin

agranulocytosis with a reduction in the number of infections and fatal complications [105]. Table 30.3 shows a summary of drugs commonly used after transplantation associated with severe neutropenia and agranulocytosis.

In transplant recipients, viral infections may lead to bone marrow suppression. Active CMV infection should be ruled out prior to stopping ganciclovir or valganciclovir in response to marrow suppression as CMV disease often presents with neutropenia and/or thrombocytopenia. Parvovirus B19, a small single-stranded DNA-virus, infects erythroid progenitor cells by binding to their cellular receptor, the P-antigen [108]. Severe and persistent aplastic anemia due to B19 infection has been reported in adult and pediatric organ transplant recipients [109]. The prevalence of symptomatic B19 infection in studies of adult solid organ recipients ranged between 1 and 2 % [110]. The prevalence in children after solid organ transplantation is unknown. The median time of presentation with B19 induced anemia after pediatric solid organ transplant is 8 months [110]. Associated thrombocytopenia and leukocytopenia are reported but infrequent. Detection of parvovirus B19 DNA in serum or bone marrow by PCR is the diagnostic gold standard, as serology is confounded by the impaired humoral response to infections. Although there is currently no specific treatment for B19 infection, IVIG has been successfully used in cases of severe anemia in immunocompromised patients [111–113]. Reduction of immunosuppression should be considered in therapy resistant cases [114].

In transplant recipients, presence of donor lymphocytes and a deregulated immune system can lead to antibody-mediated destruction of hematologic cell lines. Alloantibody-mediated hemolytic anemia usually occurs in the first weeks after solid organ transplantation [115]. This is caused by donor lymphocytes, in what is called the passenger lymphocyte syndrome whereby the concurrently transplanted B-cells produce antibodies that react against recipient red blood cell antigens [116]. Donor antibody-induced hemolysis in ABO-mismatched solid organ transplantation is usually mild and self-limiting, [117] whereas alloimmune hemolytic anemia due to antibodies with anti-D (Rhesus) specificity can be severe needing multiple transfusions [116]. Passenger lymphocyte syndrome can also affect the platelet count. Severe and resistant alloimmune thrombocytopenia with alloantibodies from passenger donor lymphocytes directed against the HPA1a-platelet antigen was demonstrated in three patients receiving kidney or liver transplantation [118]. Lacaille and coworkers described six children who developed severe antibody-mediated anemia or thrombocytopenia while treated with tacrolimus after liver or intestinal transplantation [119]. All patients had positive anti-platelet antibodies or Coombs' positive anemia. The authors suspected interference of tacrolimus with T-cell function or with endogenous control mechanisms of T-cell activation and down-regulation as the underlying mechanism. Therapy was successful with steroids or anti-CD20 monoclonal antibody [119]. In a more recent case series, four children who had undergone combined liver and bowel transplantation developed autoimmune-hemolytic anemia. Three of the four children also developed thrombi in major vessels suggesting that anticoagulation should be used when this condition presents [120].

Thrombotic microangiopathy (TMA) is a rare but potentially lethal complication encountered in solid organ transplantation. This condition encompasses the clinical diagnoses of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) and is associated with tacrolimus and cyclosporine in transplant recipients [121–123]. In severe cases, microvessel occlusion leads to tissue ischemia and organ dysfunction, which may manifest in renal failure, pancreatitis, intestinal ischemia and stroke. Besides discontinuation of the drug, plasmapheresis appears to be the most effective treatment of TMA [122, 123].

Epstein-Barr Virus and Posttransplant Lymphoproliferative Disorders

Epstein-Barr virus (EBV) is a herpes virus that can infect several cell lines including lymphocytes and has been associated with different malignancies, including post-transplant lymphoproliferative disorders (PTLD), a group of heterogeneous lymphoproliferative diseases arising in the pharmacologically immunosuppressed population

after organ transplant [124, 125]. Seronegative EBV status at time of transplant is a risk factor for PTLD, hence children are at increased risk compared to adults [126]. Generally, the risk of PTLD corresponds with the duration and intensity of the immunosuppressive therapy [126]. Specifically, the use of anti-T-cell antibodies for induction and rejection exposes intestinal recipients to a higher risk of PTLD compared to other solid organ graft recipients. The incidence is reportedly 5–10 % for intestinal recipients and appears to be higher for multivisceral recipients [21, 38, 127].

Quantitative PCR improves detection and serial monitoring of EBV viral load in peripheral blood [120, 127–129]. Since the rise of EBV viral loads often precedes the development of PTLD, have EBV DNA PCR is routinely monitored [128]. Post-transplant lymphoproliferative disorders can occur at any time, with the highest incidence occurring in the first year after transplantation [38, 124]. A high index of suspicion is needed since the clinical presentation is often nonspecific including symptoms of fever, fatigue and weight loss. Total body imaging studies with computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scan are necessary for staging of PTLD [130]. Biopsy of the accessible nodal tissues is essential, since histopathologic examination remains the gold standard for diagnosing PTLD [130]. Gastrointestinal tissue sampling may be useful in the absence of a biopsy from lymph nodes, but a negative result does not rule out the disease.

The immediate treatment of PTLD is a reduction in immunosuppression whenever feasible [124, 131]. Even temporary discontinuation of all immunosuppression with close monitoring for rejection does not lead to an increased loss of graft function in liver transplant recipients; [131] however, this aggressive approach is avoided with bowel and multivisceral transplant due to the risk of rejection. Localized disease is often successfully treated with surgery or radiotherapy along with reduction in immunotherapy [132, 133]. Subsequent treatment plans require expertise and collaborative efforts of the transplant, infectious diseases and oncology team [125]. For patients with CD20+ PTLD and who do not respond to immunotherapy reduction, rituximab provides an effective treatment [133–135]. A chemotherapy regimen of cyclosphosphamide and prednisone has been effective for refractory PTLD in children [136]. Survival after PTLD varies across centers but it is worse in disseminated disease and cases that are not controlled with reduction of immunotherapy [137, 138].

Neurological Complications

Pediatric intestinal and multivisceral transplant recipients often have significant delay in cognitive and motor function due to prematurity, malnutrition, hospitalization and severe illness in early childhood. Intraoperatively and post-transplant, they are exposed to multiple drugs with neurotoxic potential, e.g. anesthetics, tacrolimus, and corticosteroids. As a consequence, many pediatric patients display developmental delay in the first 6 months post transplant [139, 140].

After solid organ transplantation, central nervous system (CNS) complications are primarily attributable to the immunosuppressive therapy [141–145]. Cyclosporine and tacrolimus can cause a wide variety of symptoms including encephalopathy and seizures [141–145]. The diagnosis of immunosuppressant-related neurotoxicity is based on exclusion of other causes in addition to a possibly elevated serum drug concentration, but neurotoxicity can occur even without elevated serum concentrations. Treatment consists of lowering the dose or using an alternative immunosuppression. Posterior reversible encephalopathy syndrome (PRES) is associated with calcineurin inhibitors and occurs in 0.5 % of all solid organ transplants. Characterized by headache, confusion, seizure and visual loss with a specific pattern in the MRI of the brain (Fig. 30.3), PRES is frequently associated with hypertension [145]. Unrecognized, PRES may become irreversible with permanent sequelae [145]. The treatment again involves lowering the dose of the drug and treating the frequently associated hypertension. Only one adult study has examined the incidence and spectrum of neurologic complications after intestinal and multivisceral transplantation [146]. This retrospective analysis showed a high incidence of headaches (68 %), encephalopathy (43 %), and seizures (17 %) [146]. Less common were CNS infections, neuromuscular disorders, and ischemic stroke [146]. Use of ganciclovir for EBV and CMV prophylaxis appears to reduce the incidence of previously reported CNS infections. Table 30.4 provides a summary of the pathogens specifically involved in CNS infection in transplant recipients [147–151]. Neurologic complications in pediatric intestinal transplant have not been comprehensively reviewed but given the prolonged use of high dose immunosuppression are likely more common and complex than in other solid organ transplant populations.

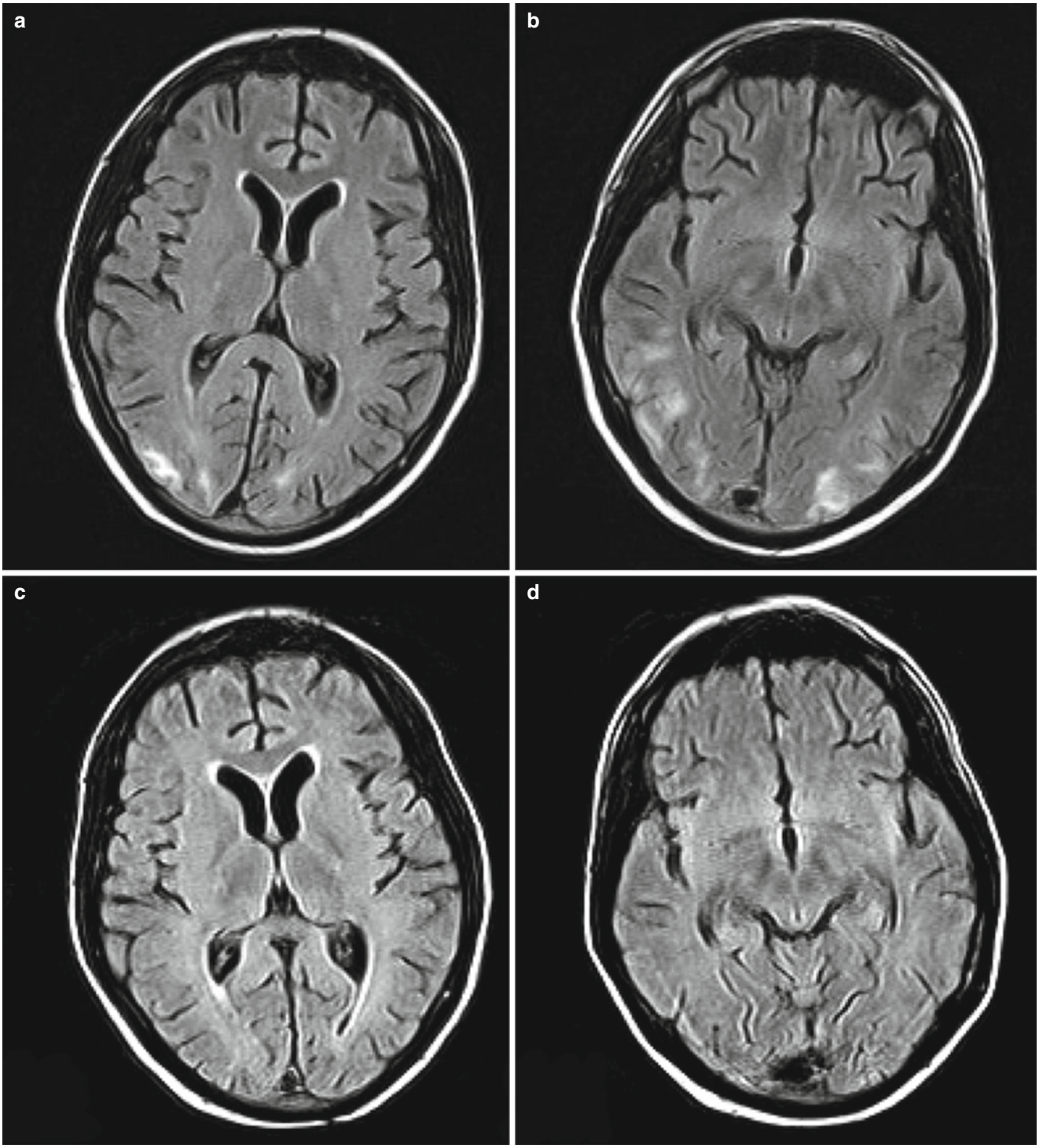

Fig. 30.3 17-year-old patient with PRES: FLAIR sequence of MRI with characteristic subcortical white matter areas of increased signal intensity in the bilateral occipital lobes (**a**, **b**). In the follow-up 16 days later the signal abnormalities are no longer visualized (**c**, **d**) (Reprinted from Hopfner et al. [152]. With permission from SAGE Publications, Inc.)

Table 30.4 Pathogens associated with CNS infections specifically in solid organ transplant recipients

Bacterial pathogens	Fungal pathogens	Viral pathogens
Nocardia	Aspergillus species	Human herpes virus 6
Listeria monocytogenes	Candida species	Cytomegalovirus
Mycobacterium tuberculosis	Cryptococcus neoformans	Epstein Barr virus
		BK virus
		JC virus

Conclusion

Improved intermediate survival after intestinal and multivisceral transplant has led to increased application of transplantation to patients with irreversible intestinal failure and an increasing number of surviving transplant recipients. The long term survival rate has remained unchanged for many years because the risk of complications remains high. Bacterial infection and ACR remain the main complications limiting life expectancy, but long-term organ dysfunctions such as chronic kidney failure impact on morbidity and mortality as short term survival improves. Only ongoing collaboration between intensivists and transplant specialists will impact both short-term and long-term complications and improve quality of life.

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Kidney Transplantation

31

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Abstract

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD) in children. Although long-term survival on dialysis has improved over the past three decades, survival remains better for children who undergo kidney transplantation. Children undergoing kidney transplantation frequently require post-operative care in the Pediatric Intensive Care Unit (PICU). For example, it is frequently necessary to infuse large volumes of fluid, plasma, and blood to prevent hypovolemia, acute tubular necrosis, and venous thrombosis of the renal allograft. These problems are compounded when a relatively young child receives an adult allograft. Because a large volume of blood is shifted to the renal allograft, the recipient's heart will have to work harder to circulate a relatively higher cardiac output (CO) to the adult-sized renal allograft. Post-operative fluid management and hemodynamic monitoring is therefore of crucial importance. Finally, there are several potential complications in the early and late post-operative period that are relevant to the pediatric critical care physician.

Keywords

End-stage renal disease (ESRD) • Chronic kidney disease • Kidney transplantation • Fluid management

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Introduction

Renal transplantation is the treatment of choice for end-stage renal disease (ESRD) in childhood. Although long-term survival on dialysis has improved over the past three decades, survival remains better for children who receive transplants [1, 2]. For example, 5-year patient survival following kidney transplantation approaches 95 % in reported series, compared to 75 % survival for children on long-term hemodialysis and 81 % for children on peritoneal dialysis [3]. Importantly, successful transplantation not only ameliorates uremic symptoms, it allows children to achieve more normal physical, cognitive, and psychosocial development. One could therefore argue that kidney transplantation affords a more normal lifestyle compared to long-term dialysis.

While renal failure remains relatively uncommon in the pediatric age group, the incidence has been increasing, particularly in adolescents. Data from the U.S. Renal Data System (USRDS) indicate that the overall incidence of

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ESRD in children is now 16 cases per one million population in the United States [3]. Congenital kidney diseases and hereditary conditions, including obstructive uropathy, congenital nephrotic syndrome, nephronophthisis, and polycystic kidney disease account for approximately 32 % of pediatric ESRD cases in North America. Glomerulonephritis (e.g., focal segmental glomerulosclerosis, IgA nephropathy, etc.) accounts for 26.1 % of cases of pediatric ESRD. Secondary causes of glomerulonephritis (vasculitis, lupus nephritis, hemolytic uremic syndrome, etc.) account for approximately 11.2 % of cases of pediatric ESRD [3]. Focal segmental glomerulosclerosis (FSGS) is one of the more frequent disorders, accounting for 11.7 % of ESRD cases [3], although it is the most common cause of ESRD in the African-American population [4].

Pre-operative Management Considerations

Urologic evaluation and surgery are often required before transplantation is considered. Children with dysfunctional bladders require careful evaluation and planning in order to avoid post-transplant urologic complications. Bladder training, intermittent catheterization, bladder augmentation, or creation of an ileal conduit or a stoma to allow for easy catheterization of the bladder (most commonly, an appendicovesicostomy) may be required. Bilateral nephrectomy may be indicated for severe vesicoureteral reflux, recurrent pyelonephritis, uncontrolled hypertension, large polycystic kidneys, intractable nephrotic syndrome or to prevent Wilms' tumor in children with Denys-Drash syndrome (male pseudohermaphroditism and glomerulopathy) [5]. In small children with a history of previous femoral hemodialysis catheters, congenital nephrosis, or laboratory evidence of a hypercoagulable state, computed tomography (CT) scan or ultrasound is advisable before transplantation to confirm patency of the iliac vessels and the inferior vena cava [6]. Absolute contraindications to transplantation are few and include active or untreated infection and malignancy.

Children with ESRD are frequently started on peritoneal dialysis (PD). If peritoneal function (i.e., removal of free water and uremic toxins) is impaired, children are at risk for cardiac failure. Such deterioration of the peritoneum occasionally occurs as a result of recurrent peritonitis or long-term PD. The peritoneal dialysis prescription, namely the frequency and content of dialysis fluid, should be altered to improve fluid removal and urea clearance. Hemodialysis (HD) should be considered if PD is ineffective and there is no improvement in cardiac function [7]. Ejection fraction (EF) monitored by echocardiography is a good index of cardiac function. An EF of more than 35–40 % pre-transplantation is expected in order to undertake renal transplant surgery safely. EF usually improves following renal transplantation when transplantation is successful (Fig. 31.1) [8].

Renal transplantation is performed preemptively (i.e., without a period on dialysis) in about 24 % of children [4]. Management of excess extracellular fluid, hyperkalemia, acidosis, and anemia are especially important for these children before transplantation. Excess extracellular fluid should be treated with loop diuretics. Potassium should be maintained within normal limits by dietary restriction, loop diuretics or sodium polystyrene sulfonate. Acidosis should be treated with sodium bicarbonate, although excess sodium intake should be avoided. Anemia should be treated with recombinant human erythropoietin with a goal hemoglobin of 10–12 g/dl. All of these considerations will optimize the patient's condition before proceeding with transplantation.

Although there are no specific age or size requirements for recipients [9, 10], individual programs usually establish their own requirements. Most centers prefer that the recipient's weight be greater than 8 kg in order to decrease thrombotic risk and accommodate for the size of an adult kidney. Several years ago it was believed that the outcomes were poor when kidneys from donors under age 6 years were transplanted into young recipients [11, 12]. However, more recent experience has demonstrated good long-term outcomes even when using young donors in the pediatric population [13, 14].

Living donors, typically a parent or another adult family member, serve as the kidney source in 37 % of pediatric transplants [4]. With rare exception, kidney donors must be 18 years of age or older. The use of a living donor is convenient, but more importantly shortens the ischemia time, often offers a better HLA match, decreases acute rejection rates, and reduces the risk for delayed graft function. Deceased donor (cadaver) kidneys are also an important resource, but availability is limited, particularly if the recipient has a more uncommon blood type (ABO type B), a history of previous transplants, or a high level of preformed antibodies to HLA antigens. Overall, in recent years in the US there has been in increase in deceased donor (DD) transplantation (and reduced time to transplant) in children, which can be attributed to the donor allocation policy developed by the United Network for Organ Sharing (UNOS) in 2005. This policy mandates that children receive priority for deceased donor kidneys from donors under 35 years of age [15].

Antibodies to donor HLA antigens are considered to be a contraindication to transplant. These antibodies may cause hyperacute or accelerated acute humoral rejections and appear to play a significant role in chronic rejection [16]. The panel reactive antibody (PRA) test is used to detect antibodies to HLA antigens, and the percentage of the panel that shows a positive antibody reaction is reported. The higher the PRA, the increased likelihood a patient will have

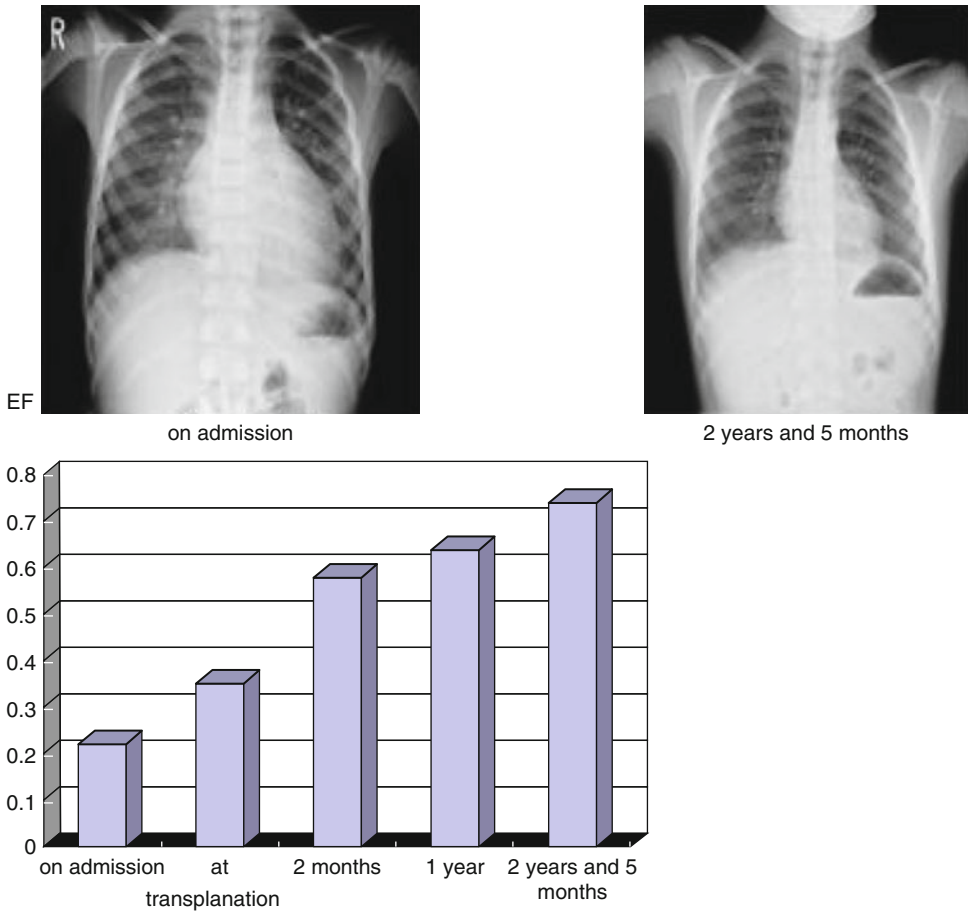

Fig. 31.1 Ejection fraction and chest radiograph before and after kidney transplantation in a child with dilated cardiomyopathy

a positive lymphocyte crossmatch against a potential donor. Strategies for removing or suppressing HLA antibody production, including plasmapheresis, rituximab, and administration of high-dose intravenous immunoglobulin, have been used with some success [17, 18]. Recipients who have received multiple blood transfusions (>5) pre-transplantation have a graft failure rate increase up to 30 % compared to recipients who received fewer than five transfusions [19]. For this reason (among others), a conservative transfusion policy (i.e., transfusion threshold for Hb $\leq$7.0 g/dL) is recommended.

Surgical Considerations

Small children, less than 20 kg, are at increased risk of arterial and venous thrombosis and require high blood flow to the kidney in order to minimize this complication [20]. Consequently, the kidney is anastomosed typically to the distal aorta and adjacent inferior vena cava, with care being taken to avoid redundancy of the renal vein and tension on the renal artery anastomosis [21]. The procedure can be performed through either a transperitoneal or a retroperitoneal approach. In general, the right retroperitoneal approach is technically feasible in the vast majority of cases, provides easy access to the kidney for percutaneous biopsy, and minimizes the risk of subsequent gastrointestinal complications [22, 23]. Transplants into larger children are performed in a manner similar to that used for adults. An oblique lower abdominal retroperitoneal incision allows the artery and vein to be anastomosed to the iliac vessels. Irrespective of the approach, careful ligation of lymphatic and adipose tissue around the vessels is necessary to reduce the risk of a post-transplant lymphocele.

Intra-operative Management

In the operating room (OR) strict attention to intravascular volume status is essential to ensure adequate perfusion of the new kidney once the vascular clamps are removed to prevent donor graft failure. Hemodynamic monitoring is critical during the intra-operative period. In general this should include routine arterial blood pressure and central venous pressure (CVP) monitoring at a minimum, though some authorities recommend additional monitoring with trans-esophageal echocardiography [24], continuous cardiac output monitoring (there are several commercially available devices based

upon either thermodilution or pulse contour analysis for this purpose), and central venous oxygen co-oximetry (as a surrogate for mixed venous oxygen saturation). Crystalloid and colloid solutions are used in the OR to elevate the recipient's CVP to 10–15 cmH_2O prior to release of the vascular clamps. Higher CVP goals have been reported in the literature for small infants receiving an adult sized kidney transplant [25]. If a small child receives an adult kidney, a significant proportion of the recipient's cardiac output is shunted to the relative large donor kidney. These children may require large volumes of both crystalloid and colloid in order to perfuse the large (relative to the size of the child) allograft. If blood circulation to a renal allograft is not sufficient, delayed graft function due to acute tubular necrosis or renal vein thrombosis can occur.

Urine output is stimulated by the infusion of mannitol and furosemide just before the vascular clamps are removed. At some centers verapamil may be injected into the renal artery to reduce vasospasm [26]. Inotropic support may be indicated if baseline myocardial function is impaired, as discussed above [27]. Generally a large dose of methylprednisolone is administered in the operating room prior to completion of the vascular anastomosis. Depending on the center's protocol, additional immunosuppressive agents may also be administered in the OR.

Post-operative Management Considerations

With a living- related transplant, urine output is almost immediate and may be copious but immeasurable until the ureteral anastomosis is complete. Once feasible, urine replacement should be fastidious to avoid hypovolemia. The replacement fluid can be tailored to match the urine electrolytes, but typically 0.45 % saline is used. Children with living donors usually have polyuria and frequently develop glucosuria and osmotic diuresis if dextrose-containing fluids are used for urine replacement. Caution is advised in administering potassium, as urine potassium losses may not be high even with a brisk diuresis. Measurement of the urine potassium can help in determining how much potassium to add to the replacement fluids. Close monitoring of the electrolytes is recommended for the first 24–48 h (i.e., every 6 h the first day and then every 12 h if stable), as hypocalcemia, hypomagnesemia, and hypophosphatemia may develop. Insensible fluids (based on weight) containing dextrose should be administered post-operatively in addition to urine replacements. As kidney function begins to improve, the serum creatinine will decrease, the urine will become more concentrated, and the urine output will start to match the daily intake. Although most children are tracheally extubated in the OR prior to transfer to the PICU, infants and small children may require ventilation for a period of time after surgery [28]. Adequate pain control with narcotics should be achieved to allow for good pulmonary toilet and to prevent atelectasis.

After the recipient arrives in the PICU, the urine output should be monitored along with the vital signs and CVP, if available. If the urine output falls (along with the CVP), fluid boluses with 5–10 mL/kg of 0.9 % saline or 5 % albumin should be used to boost intravascular volume. If volume repletion does not enhance output, intravenous (IV) furosemide 1–2 mg/kg can be administered. If the response to these interventions is poor, immediate consultation with the transplant surgeon or nephrologist is indicated. Occlusion of the urethral catheter by a blood clot is a common problem and should be excluded by irrigating the catheter with 10–20 mL of saline. As mentioned earlier, some children may benefit from an inotropic agent secondary to impaired cardiac function [27]. Renal artery flow, in the first 3 days post transplantation, does not increase with low-dose (so-called "renal dose") dopamine [29]. Therefore routine use of dopamine is not indicated unless required to support the systemic blood pressure. Denervation of the transplant exists for several months and likely contributes, along with other factors, to this insensitivity [30].

Some patients will develop significant hypertension immediately post-transplantation and require treatment. The decision to begin antihypertensive medications should be made in conjunction with the transplant team. Pain is a common source of hypertension and should be well controlled in the post-operative period. Antihypertensive medications should be initiated cautiously to avoid a marked drop in blood pressure and perfusion of the kidney. In case of overtreatment or a change in patient status, short-acting intravenous preparations are preferred initially. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are not used during the immediate post-transplantation period because of the potential effects on renal function and perfusion. Other classes of antihypertensive medications can be used safely, with the one notable exception of nicardipine, which has been shown to increase the risk of tacrolimus-mediated nephrotoxicity [31, 32].

Fever during the immediate post-transplantation period may be a manifestation of infection or a side effect of antilymphocyte therapy. Infections occurring during the first few days following are usually of bacterial etiology and related to the surgical procedure, indwelling dialysis catheters, intravenous lines, poor pulmonary toilet, and urinary catheters. The possibility of an incompletely treated infection pretransplantation should also be considered, particularly for patients with indwelling dialysis catheters. Rarely, bacterial or fungal infections may be transmitted from the donor [33]. After an appropriate evaluation is completed, initiation of broad-spectrum antibiotics may be indicated depending on the status of the child. Antibiotics should be selected

carefully, considering the possibility of drug interactions, nephrotoxicity, and the need to adjust dosing for changing renal function.

Surgical Complications

Fortunately, serious surgical postoperative complications are not common but include vascular thrombosis, ureteral obstruction, or urinary leak. For small children with output from native kidneys, a Doppler ultrasound post-operatively is helpful in confirming adequate perfusion of the graft. In patients with adequate urine output and decreasing serum creatinine, routine evaluation by ultrasound can be deferred [34]. However, when there is no urine output in a living donor transplant or an abrupt reduction in output (regardless of donor source), prompt evaluation with ultrasound for complications should be considered if initial efforts to restore urine output are unsuccessful. The need for close communication and collaboration between the intensivist, the surgeon(s), and the nephrologist cannot be overemphasized.

Vascular Thrombosis

Vascular thrombosis continues to be a significant problem in pediatric transplantation, accounting for nearly 10 % of allograft failures [4]. Unfortunately, when vascular thrombosis occurs, the effect is usually catastrophic as prompt action is required and recognition may be delayed. Generally, vascular thrombosis develops during the first 24–48 h following transplantation, though vascular thrombosis can occur up to 7–15 days post-transplantation [35].

Early thrombosis is more likely in small children and infants, particularly if systemic blood pressure and CVP are not adequately maintained. An adult kidney typically holds up to 150–200 mL of blood [27]. The aortic blood flow doubles when an adult kidney is transplanted into an infant, but renal artery flow only reaches about half of normal adult renal artery flow [20]. To maximize perfusion of the kidney, intravascular volume must be closely monitored and maintained.

Risk factors for vascular thrombosis include recipient age under 2 years, donor age under 6 years, prolonged cold ischemia time (greater than 24 h), prior transplantation, the presence of antiphospholipid antibodies, and pre-transplantation peritoneal dialysis [11, 36–40]. Chronic peritoneal dialysis may induce a hypercoagulable state, which therefore increases the risk of vascular thrombosis [38]. Maneuvers to prevent thrombosis in the immediate perioperative period could include the prophylactic use of heparin and/or aspirin. Concerns regarding the routine use of heparin include an increased risk for hemorrhagic complications and conflicting results on efficacy [41, 42]. Low dose aspirin therapy has been found to be safe and effective in adults, but has not been thoroughly evaluated in children [43, 44]. A retrospective analysis of a large transplant database suggested that the use of IL-2 receptor antagonists (for immunosuppression) was correlated with reduced graft failure secondary to thrombosis, but further clinical correlation is needed [45].

Ureteral Obstruction and Urinary Leak

Urologic complications are not common early in the postoperative course. Ureteral obstruction caused by edema, blood clot, or peritransplantation fluid collection should be considered if there is an unexplained fall in urine output. A urinary leak may occur at the site of the ureteral implant, the bladder wall incision, or at the ureterovesical junction secondary to compromise of blood supply to the distal ureter with resulting necrosis, or from a renal calyx because of back pressure from ureteral obstruction. Renal ultrasound and radionuclide scans are useful in evaluating for these complications. If a wound drain is present, simultaneous analysis of fluid from the drain and blood for urea nitrogen and creatinine will aid in determining whether a peritransplant fluid collection represents lymph, blood, or urine. Ureteral stents, left in place for 3–6 weeks, reduce stress on the ureterovesical junction and lessen the risk of acute obstruction secondary to edema. Maintenance of a urethral catheter for several days post-transplantation further lessens the chance of a urinary leak. Lymphoceles (collection of lymph around the transplant) may occur in up to 0.8 %–18 % of transplants but are usually asymptomatic and develop several weeks after the procedure [46]. Treatment is usually not necessary unless the collection is quite large and causing pain or ureteral obstruction. Lymphoceles may be marsupialized into the peritoneal cavity, commonly by a laparoscopic approach.

Bleeding

Bleeding from vascular anastomotic sites is very rare. Peritransplant hematomas may occasionally develop and should be drained surgically if the bleeding persists or the collection is compromising the patency of the vessels or the ureter. Rupture of the transplant may rarely occur secondary to venous thrombosis or acute rejection.

Acute Tubular Necrosis

Although delayed graft function may occur immediately post-transplantation for a variety of reasons, acute tubular necrosis (ATN) is the most common etiology. Risk factors for ATN include deceased donor transplant, repeated transplants, more than five blood cell transfusions pre-transplantation, and cold ischemia time greater than 24 h. It has been suggested that laparoscopic retrieval of living donor kidneys may also increase the risk for delayed graft function, especially in children 5 years of age and younger [47]. Once a presumptive diagnosis of ATN is made, adequate arterial and central venous pressures should be maintained, and furosemide

can be administered to stimulate urine output. If there is no response, diuretics should be discontinued. During this period careful conservative management of renal failure is indicated. Dialysis should be avoided if possible for the first 24 h post-transplantation, but can be performed subsequently when indicated. Use of sodium polystyrene sulfonate (SPS or Kayexalate) should be withheld until good bowel function is reestablished. In adult recipients, constipation and the administration of SPS have been suggested as risk factors for colonic necrosis and perforation [48, 49].

Acute tubular necrosis typically lasts 1–7 days but may persist for up to 4 weeks [50]. During prolonged ATN it is important to remain vigilant for other complications, including vascular thrombosis and acute rejection. Periodic allograft biopsies are indicated during prolonged (greater than 5 days) ATN to screen for acute rejection. Although most kidneys recover from ATN, long-term allograft survival is significantly shorter compared with kidneys without a delay in function. Primary non-function (kidneys that never make any urine) occurs uncommonly and accounts for only 2.2 % of graft failures [4].

Immunosuppression

As soon as the allograft is reperfused the risk for rejection exists. Rejection is a complex process in which both antibody and cell mediated immunity may play a role. Hyperacute or immediate rejection, caused by antibodies to HLA antigens or blood group ABO, is almost never seen because of the use of a pre-transplantation lymphocyte cross-match and ABO compatible donors. Acute cellular rejection is diagnosed most frequently and occurs because of activation of recipient T lymphocytes by donor HLA antigens. Acute rejection occurs in approximately 15 % of transplants [4]. Once activated, T cells undergo clonal expansion, produce cytokines, and differentiate into CD8+ and CD4+ lymphocytes. Through a cascade of events, T cell–mediated graft rejection leads to destruction of graft cells by CD8+ CTL (cytotoxic T lymphocytes) and stimulation of B cell antibody production and induction of delayed hypersensitivity responses by activated CD4+ helper cells. Acute cellular rejection is characterized by infiltration of the interstitium and tubule cells by mononuclear cells and occasionally eosinophils. Antibody mediated rejection is characterized by vascular rather than tubular involvement. Cellular and humoral rejection may coexist.

Antirejection therapy is typically initiated immediately prior to transplant or in the operating room. Induction therapy with antilymphocyte or anti-interleukin 2 (IL-2) receptor antibodies are used in less than 50 % of transplants [4]. Maintenance immunosuppression typically consists of two or three oral medications. The combination of drugs employed varies among centers. Because of undesirable side effects, protocols that minimize exposure to corticosteroids or calcineurin inhibitors (cyclosporine and tacrolimus) have been under investigation [51–53]. Steroid sparing regimens have been of particular interest in the pediatric age group due to issues with growth retardation and alteration in physical appearance. Recent publications have described the safe use of complete steroid avoidance in patients receiving their first transplant, while ameliorating the effects of steroid therapy [54–56]. A recent analysis of data from the United Network for Organ Sharing database revealed that the use of steroid free maintenance immunosuppression in pediatric recipients had increased from 8.7 % in 2002 to 37 % in 2009 [54]. Monitoring of drug levels is critical in the management of transplant recipients. The target levels will vary depending on the combination of drugs being utilized and the transplant protocol. The pharmacology of the commonly used immunosuppressive medications is discussed later in this section.

Most maintenance immunosuppression protocols include one of the calcineurin inhibitors (CNI). Of the calcineurin inhibitors, the less nephrotoxic tacrolimus (TAC) is the most commonly used [4]. Initiation of TAC therapy is delayed until good renal function is established. Trough levels of TAC are monitored to assess dosing adequacy and, unlike cyclosporine (CsA), accurately reflect drug exposure [57]. Tacrolimus is extensively metabolized by the cytochrome P450 system and important drug interactions exist. As experience with TAC has been gained, the suggested target levels have been lowered, resulting in a reduction in adverse events, including nephrotoxicity, post-transplantation lymphoproliferative disease, opportunistic infections, and post-transplantation diabetes mellitus. It should be noted that marked elevation of TAC levels may occur during episodes of gastroenteritis [58].

Azathioprine (AZA) has largely been replaced in transplantation protocols by mycophenolate mofetil (MMF), which has a similar mechanism of action [4]. MMF is a more powerful immunosuppressant than AZA but has fewer hematologic side effects. Diarrhea is the most common side effect of MMF and may be severe enough to prompt a reduction in dose or discontinuation of the medication. Enteric coated mycophenolic acid has been reported to improve gastrointestinal tolerability and has been used with success in older children who can take pills [59]. MMF inhibits inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the de novo synthesis of purines. After ingestion MMF is rapidly metabolized to its active form, mycophenolic acid. The role of therapeutic drug monitoring of mycophenolic acid levels in renal transplantation remains controversial. Although those who support such testing advocate that surveillance will allow avoidance of under- or overimmunosuppression [60, 61], currently dosing based on levels is not routinely utilized.

Sirolimus (SRL) was a widely used drug at the start of the century, approximately 25 % of transplant recipients were taking this agent at 30 days post-transplant in 2002. Recent evidence has shown a strong association of post-transplantation lymphoproliferative disorder (PTLD) with the use of SRL so its use in kidney transplantation is limited [62]. From 2003 to 2010, the most common drug combination at 30 days post-transplant was tacrolimus/MMF/Prednisone (56 %) and tacrolimus/MMF (14.8 %) [4].

Polyclonal antibodies against T cells (antithymocyte globulin[equine] and antithymocyte globulin [rabbit]) have been used extensively in transplantation. Administration of these agents leads to long-lasting T-lymphocyte depletion. These agents may be given as part of induction therapy to prevent rejection or for treatment of acute rejection. MMF, SRL, and AZA are generally discontinued during the course of treatment; CsA and TAC can be omitted or given in a low dose [53]. Side effects include anaphylaxis, thrombocytopenia, neutropenia, excessive immunosuppression leading to infections, serum sickness, and an increased risk for lymphoma or PTLD. Dose adjustment may be required for leukopenia and thrombocytopenia. Basiliximab is a monoclonal antibody produced by recombinant DNA technology that binds to the interleukin- 2 receptor **α**-chain on the surface of activated T lymphocytes. Basiliximab is given at the time of transplant and again on the fourth postoperative day. Although severe acute hypersensitivity reactions may occur rarely, few side effects have been reported with this medication [63]. Noncardiogenic pulmonary edema has been reported in a few adolescent renal transplant recipients after receiving basiliximab [64]. The humanized anti-CD52 monoclonal antibody alemtuzumab (Campath-1H), has been used in induction therapy and may have a role in the treatment of acute rejection [65, 66]. Treatment leads to marked and long-lasting depletion of T lymphocytes with a lesser effect on B lymphocytes, natural killer cells and monocytes. Rituximab is a monoclonal antibody directed against the CD20 antigen on B lymphocytes. Rituximab treatment results in B lymphocyte depletion and has been used in renal transplant recipients to reduce high levels of HLA antibodies, and to treat antibody-mediated rejection, and post-transplantation lymphoproliferative disease [18, 67–69].

Long-Term Complications

Acute Rejection

Although acute rejection may occur at any time, the greatest risk exists during the first 3–6 months post-transplantation. Risk factors for acute rejection include deceased donor kidney, age (>12 years old has highest risk, lowest risk in 0–1 years old), and delayed graft function [4].

With current immunosuppression protocols the majority of children experience no acute rejection episodes. For children receiving a kidney transplant between 2007 and 2010, the 12-month probability of experiencing an acute rejection was 8.6 % for living donor recipients and 16.6 % for deceased donor recipients [4]. Acute rejection was the second most common cause of transplantation failure, accounting for 13.2 % of graft losses [4].

With the advent of new potent immunosuppressive medications, acute rejection is typically asymptomatic in older children and adolescents and is detected because of an unexplained rise in the serum creatinine. However, in infants and small children, rejection of a relatively large adult kidney may result in symptoms including fever, chills, oliguria, or hypertension. In a small child with an adult size graft it should be appreciated that significant compromise of the organ must occur before it is reflected in the serum creatinine level. Acute rejection may be suspected on clinical and laboratory data, but the gold standard for diagnosis remains percutaneous renal biopsy.

The first line therapy for acute cellular rejection usually consists of high dose IV methylprednisolone (10–30 mg/kg/day) for 3–5 days, with response seen in about 75 % of episodes [24, 53, 63]. Steroid-resistant rejections are often responsive to treatment with lymphocyte depleting antibodies such as antithymocyte globulin. After reversing an acute rejection, alteration in the maintenance immunosuppressive regimen to include more potent agents should be considered. Antibody mediated rejection (AMR) is being recognized more frequently and has been estimated in 3–10 % of transplants [70]. Positive staining for C4d, a degradation product of the classical complement pathway, around the peritubular capillaries has emerged as an important clue to the presence of AMR [17, 71]. Improved detection of donor specific antibodies as well as better definition of histologic changes associated with AMR has resulted in greater recognition of AMR [71]. Routine treatment with high dose corticosteroids is less effective in this type of rejection. Various protocols involving the use of plasmapheresis, immunoadsorption with protein A, IV immunoglobulin, and rituximab have been developed and used with varying success [17, 69, 72–74]. Eculizumab, an antibody to complement protein C5 that acts to inhibit formation of the membrane attack complex, may also prove useful in treating AMR though data is limited at this time [75].

Chronic Rejection

Although progress has been made in preventing acute rejection, similar success has not been achieved in preventing chronic rejection. Chronic rejection (chronic allograft nephropathy or CAN), is the most common cause of allograft

failure in adolescents and children and accounts for 35.6 % of graft losses [4]. Chronic allograft nephropathy is characterized by glomerular sclerosis, tubular atrophy, interstitial and vascular fibrosis, and a nonspecific focal interstitial infiltrate of lymphocytes and plasma cells. Chronic allograft nephropathy may be detected as early as 1 month post-transplantation [76] and is suspected because of a progressive rise in the serum creatinine level, which is often associated with proteinuria and hypertension. Although acute rejection is a risk factor for CAN, nonimmunologic factors such as delayed graft function, glomerular hyperfiltration, calcineurin inhibitor toxicity, hyperlipidemia, and hypertension have been implicated as well [76]. Therapeutic options in CAN are limited and may include a change from CsA to TAC, TAC to SRL, or AZA to MMF [52]. Treatment of hypertension with ACE inhibitors may be beneficial in the setting of CAN [76]. Treatment with oral or IV corticosteroids is not indicated unless acute rejection is also present.

Hypertension

After receiving a transplant 50–80 % of children experience hypertension as defined by the use of an antihypertensive medication or blood pressure >95th% for age and height [77, 78]. Factors associated with hypertension include corticosteroid exposure, CsA or TAC use, impaired transplant function, renal artery stenosis, acute rejection, chronic allograft nephropathy, and renin release from native kidneys. Persistence of hypertension negatively affects long term transplant outcome [77]. In addition to optimization of blood pressure control, ACE inhibitors and ARBs may be particularly beneficial in preserving transplant function [77, 78]. Although not used in the immediate postoperative period, ACE inhibitors and ARBs can be initiated safely 2 weeks or more post-transplantation. In patients with unsuspected transplant artery stenosis, these agents may cause renal failure, so follow-up measurement of the serum creatinine level within days to a week after initiation is indicated.

Seizures

Seizures occur most frequently in the first 6 months after transplantation. A recent single center study found that 6 % of children will experience one or more seizures post-transplantation [79]. Typically the etiology of the seizures is multifactorial. Hypertension, along with other factors such as electrolyte disturbances, fever, infection, and therapy with CsA or TAC may play a significant role. Although seizures are a common complication in dialysis patients, a history of seizures pre-transplantation is not a risk factor for seizures post-transplantation [80] and long-term anticonvulsant therapy is usually not necessary. Reversible posterior leukoencephalopathy has been reported in post-transplantation patients and has been associated with hypertension and CsA and TAC therapies. Although more common with elevated drug levels, neurotoxicity may occur with CsA or TAC levels in the target range. With aggressive treatment of hypertension, CNI can often be continued [81–83].

Infections

Infections are the second most common reason for hospitalization post-transplantation and the leading cause of mortality [4]. Because of improved immunosuppression, fever in a transplant recipient is usually caused by infection rather than rejection. Early, during the first month after surgery, bacterial and fungal infections predominate [33]. Indwelling urinary, peritoneal, or hemodialysis catheters, wound drains, central and peripheral vascular access catheters, and poor pulmonary toilet pose risks as they would for an immunocompetent individual. After the first month, opportunistic infections may develop as the recipient is now immunosuppressed. Important factors contributing to infection include epidemiologic exposures and the net state of immunosuppression [33]. Over time, the risk for opportunistic infections lessens if the patient does well and immunosuppression can be tapered to minimal levels. After the perioperative hospitalization viral upper respiratory infections and otitis media were the most common causes of infection in pediatric renal recipients [84]. These infections occurred at a similar frequency to that observed in normal children. Urinary tract infections also remain a risk beyond the perioperative period [84–86], particularly in those with an abnormal urinary tract [86]. Infections in immunosuppressed patients are discussed in much greater detail elsewhere in this textbook.

Polyomavirus (BK) Nephropathy

Polyomavirus (BK) infection is a trivial illness in the normal host and occurs in virtually all children by age 10 years [87]. After the initial infection, the virus remains latent in the urinary tract. In the setting of aggressive immunosuppression, BK virus proliferates and may cause an acute tubulointerstitial nephritis (BK nephropathy, BKN) or ureteral stenosis. The appearance of BKN on biopsy mimics acute rejection and may lead the transplant physician to increase immunosuppression at a time when a reduction in immunosuppression is indicated. BK infection is not uncommon, and its significance as a cause of transplant failure has been appreciated only in recent years. Screening for BKN can be performed with urine cytology or quantitative PCR of urine and/or blood, but ultimately confirmation of kidney tissue involvement with immunohistochemical staining or in situ hybridization is required to make the diagnosis. The initial

step in management is reduction of immunosuppression. Other therapeutic options include treatment with quinolone antibiotics, leflunomide, and IV immunoglobulin and cidofovir [88–90].

Recurrence of Primary Disease

Intensivists should also be aware that some primary renal diseases may recur in the transplant, including several types of glomerulonephritis, primary hyperoxaluria, and hemolytic uremic syndrome. Recurrence of the primary disease is reported to account for 6.9 % of transplant failures [4]. In particular, FSGS, a common cause of ESRD, may recur in up to 59 % of renal transplants and is associated with ATN and decreased graft survival [91–96]. Recurrence of FSGS is thought to be caused by a circulating factor that increases the permeability of the glomerular basement membrane to protein [97]. Identification of the circulating factor is not certain, but one candidate is soluble urokinase receptor [98]. The effect of immunosuppression on the production or action of circulating factor(s) remains unclear as does the exact mechanism through which this protein increases the permeability of the glomerular basement membrane. Plasmapheresis has been found to be beneficial and may be employed to treat or prevent recurrence [91–93, 96, 99, 100]. Profound proteinuria and nephrotic syndrome may develop within hours or days of the transplant. Prompt recognition of recurrence of the nephrotic syndrome is critical as early initiation of plasmapheresis is more likely to result in successful treatment [93, 94]. If plasmapheresis is not successful, adjunctive therapeutic measures most commonly utilized include pulse methylprednisolone, rituximab, cyclophosphamide, high-dose CsA, and ACE inhibitors [91, 101–103]. If treated successfully, transplant survival in children with recurrence is reported to be similar to those without recurrence [94, 96].

Long-Term Outcome

With advances in immunosuppressive therapy, short-term (1-year) graft survival is 96.5 % living donor kidneys and 95.1 % for deceased donor kidneys [4]. Unfortunately, improvement in long-term survival has been more difficult to achieve. Five-year allograft survival rates for transplantations performed in recent years are 78 % for deceased donor and 84 % for living donor transplants [4]. Adolescents have the highest risk of rejection. It has been suggested that multiple factors contribute to graft loss in older children, including poor compliance [4]. Determination of the factors contributing to the poor outcome in some groups may allow modification of transplant protocols with eventual improvement in allograft survival.

Despite improved patient and allograft survival rates, cardiovascular disease has been identified as a factor limiting rehabilitation of the pediatric ESRD population. Although transplant recipients fare better than those on dialysis, cardiovascular disease is the leading cause of death in the transplant population [104]. Even after a successful transplantation, the risk for death from cardiovascular disease remains greatly above the risk for normal children (22 % versus 3 %) [104]. Children and adult survivors of pediatric ESRD are at risk for arrhythmias, myocardial infarction, cardiomyopathy, and sudden cardiac death [105]. Factors contributing to cardiovascular disease in this population include hypervolemia, hypertension, left ventricular hypertrophy, left ventricular dysfunction, hyperlipidemia, vascular calcifications, anemia, hyperglycemia/insulin resistance, malnutrition, hyperhomocysteinemia, and chronic inflammation [105, 106]. Efforts should focus on amelioration of these risk factors in order to enhance the long-term outlook for these young people.

Conclusion

The care of children and adolescents with kidney transplants is complex and requires an integrated team of physicians, including the transplant surgeon, urologist, nephrologist, intensivist, and anesthesiologist. Although substantial improvements have been made in the arena of pediatric renal transplantation, many challenges remain.

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Index

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