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Irwin & Rippe's Manual of Intensive Care Medicine

SIXTH EDITION

Richard S. Irwin
Craig M. Lilly
James M. Rippe

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IRWIN & RIPPE'S MANUAL OF INTENSIVE CARE MEDICINE

Sixth Edition

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Preface

We are delighted to present the sixth edition of the *Manual of Intensive Care Medicine*. Previous editions have established this *Manual* as a leading source of information in the ever-evolving, diverse, and complicated field of critical care and intensive care medicine. The practical format and user-friendly, portable size of the *Manual* have made it a particularly valuable aid in the bedside practice of intensive care and a valuable reference for students, interns, residents, fellows, nurse practitioners and physician assistants, nurses, and respiratory care practitioners practicing in the critical care medicine environment.

As in the previous edition of this work, the sixth edition of the *Manual* is intended to parallel our major textbook *Irwin and Rippe's Intensive Care Medicine*. This latter, hardcover book is now in its seventh edition and continues to be a leading source of intensive care knowledge both in the United States and throughout the world.

We are pleased to announce that the sixth edition of the *Manual* will be available not only in print but also online and as an app for e-readers. Choice of format allows busy bedside providers access to the information they need the way they like to receive it. These resources allow immediate access to the information that allows busy professionals to optimally manage the complicated issues encountered in the care of critically ill adults. As in previous editions, we have challenged the section editors and authors to not only update all the content contained within the *Manual*, such as the important role that bedside ultrasonography plays in caring for the critically ill, but also emphasize salient concepts and focus on key, clinically relevant points. Annotated references are provided at the close of each chapter to guide the interested reader through key articles in the relevant literature. Each chapter reflects the best available evidence with a focus on patient safety, and, where appropriate, videos have been added to exemplify points and findings.

The *Manual of Intensive Care Medicine* opens with an extensive section on Procedures and Techniques. The remaining 15 sections are divided among organ system problems and other common and important issues, such as palliative care and ethical issues, and transplantation. In each chapter within these sections, discussions of key conditions that present in the intensive care unit environments are presented together with targeted discussions focusing on treatment.

We are delighted to welcome new section editors in the following areas: Dr. Gail Scully in Infectious Disease Problems; Dr. Samir Malkani in Endocrine Problems; Dr. Timothy A. Emhoff in Shock and Trauma; Dr. Sonia Chimienti, who joined Dr. Christoph Troppmann as a co-section editor in the Transplantation section; and Dr. Jennifer Reidy, who is the section editor of a new section in the book on Palliative Care and Ethical Issues in the Intensive Care Unit.

As in the previous edition, the management of overdoses and poisonings is covered so comprehensively in the Pharmacology, Overdoses, and Poisonings section that the section mimics a textbook unto itself. For this, we have special thanks to the section editor Luke Yip, who created the easy-to-use tabular format of this section. We are also indebted to our other section editors who have continued to contribute in an extraordinary way by updating their sections: Dr. Stephen O. Heard, who has overseen the Procedures and Techniques and Minimally Invasive Monitoring section; Dr. Akshay S. Desai, Cardiovascular Problems and Coronary Care; Dr. J. Mark Madison, Pulmonary Problems; Dr. Pang-Yen Fan, Renal Problems; Dr. Dominic J. Nompleggi, Gastrointestinal and Hepatobiliary Problems; Dr. Patrick F. Fogarty,

Hematologic Problems; Dr. Fred A. Luchette, Surgical Problems; Drs. David Paydarfar and David A. Drachman, Neurologic Problems; Dr. Paul F. Dellaripa, Rheumatologic and Immunologic Problems; Dr. John Querques, Psychiatric Issues; and Dr. Joseph Frassica, Appendix.

We wish to acknowledge that many of the chapter authors for the current *Manual* have also made major contributors to our larger-format textbook, *Irwin and Rippe's Intensive Care Medicine*. Although the *Manual of Intensive Care Medicine* has been edited and revised with the expert guidance of many section editors, many of the chapters were developed based on the expert knowledge of the original textbook contributors, reorganized, and rewritten in a style necessary for the scope of this portable text.

We also wish to once again acknowledge and thank a number of individuals without whose assistance the sixth edition of this *Manual* would not have been possible. First and foremost, Dr. Rippe's Editorial Director, Elizabeth Grady, who continues to do a superb job in organizing and expediting all aspects of the manuscript preparation for this book and many others. Without Beth's superb editorial skills, projects such as this would not be possible. Gina Giangregorio and Linda Doherty, Dr. Irwin's and Dr. Lilly's administrative assistants, and Cynthia French, Dr. Irwin's clinical coordinator, also have provided important assistance in managing their complex clinical and academic endeavors. Carol Moreau, executive assistant to Dr. Rippe, expertly juggles the diverse aspects of his clinical, research, and travel calendar to carve out time for projects of this magnitude. Debra Adamonis, office assistant to Beth Grady and Carol Moreau provides wonderful daily logistical support.

A special word of thanks to the editorial team members at Lippincott Williams & Wilkins, who support all of our medical editing projects and have supported the process every step of the way. We wish to particularly thank our Senior Acquisitions Editor, Brian Brown, for his support throughout the process of writing this book. Nicole Dernoski, Senior Product Manager, also provided logistical support and expertise throughout the editorial process on this and previous editions of the *Manual*.

Finally, we wish to thank our families: Diane Irwin; Rachel, Andrew, Truman, and Bailey Koh; Sara, Benjamin, Jacob, and Isaac DiIorio; Jamie, Andrew, Emmett, and Asher McIntosh; Rebecca and Adam Slater; Stephanie, Hart, Jaelin, Devon, and Jamie Rippe; and Leslie, Jonathan, and Catherine Lilly, who continue to love and support us in all of our efforts, both personal and academic, and make it all worthwhile.

Richard S. Irwin, MD
Craig M. Lilly, MD
James M. Rippe, MD

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Section Editor - Paul F. Dellaripa

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Appendix

SECTION 1

Procedures and Techniques and Minimally Invasive Monitoring in the ICU

Stephen O. Heard

1

Airway Management and Endotracheal Intubation

Elifce O. Cosar and Adam D. Currier

I. GENERAL PRINCIPLES

A. Maintenance of adequate ventilation and pulmonary gas exchange is very important in critically ill patients. Airway management in intensive care patients differs significantly from routine surgical procedures in the operating room.

B. Critical care physicians should be familiar with the equipment and the techniques to maintain and secure the airway.

II. ANATOMY.

The airway is divided into the upper airway and lower airway.

A. Nose.

The nose serves a number of functions: respiration, olfaction, humidification, filtration, and phonation.

B. Pharynx.

The pharynx extends from the base of the skull to the level of the cricoid cartilage.

C. Larynx.

1. The larynx lies in the adult neck opposite the third through sixth cervical vertebrae.
2. The laryngeal skeleton consists of hyoid bone and nine cartilages. These are the unpaired thyroid, cricoid, and epiglottis and the paired arytenoid, corniculate, and cuneiform cartilages. The cricoid cartilage is the only structure that completely encircles the airway.
3. Two nerves that are branches of the vagus innervate the larynx.
   a. The external branch of superior laryngeal nerve supplies motor innervation to the cricothyroid muscle. All other motor supply to the laryngeal muscles is provided by the recurrent laryngeal nerve.
   b. The internal branch of the superior laryngeal nerve provides sensation above the cords. Sensory innervation below the cords is supplied by the recurrent laryngeal nerve.

D. Trachea.

1. The adult trachea begins at the cricoid cartilage. It is 10 to 20 cm long.
2. It divides into right and left main bronchi at the level of fourth and fifth thoracic vertebrae. The right main bronchus is wider and shorter and takes off at a less acute angle than the left, thus making right main bronchus intubation more likely.

III. EVALUATION OF THE AIRWAY

A. Several clinical criteria can be assessed.

1. Mouth opening.
2. Mallampati classification (Fig. 1-1).
3. Head and neck movement.
4. Ability to prognath (i.e., to bring the lower incisors in front of the upper incisors).
5. Thyromental distance.
6. Body weight.
7. Neck circumference.
8. Previous history of difficult intubation (single most reliable predictor of a difficult airway).

B. Difficult airway in some patients will remain undetected despite the most careful airway examination.

C. Cervical collars, halo devices, trauma to the mandible or neck, morbid obesity, pregnancy, acromegaly, burns, and obstructive sleep apnea may signal a difficult airway.

D. Age >55, body mass index >26, snoring, presence of a beard, lack of teeth, Mallampati class III or IV, abnormal mandibular protrusion test, and male gender are independent clinical risk factors for difficult mask ventilation.

IV. AIRWAY EQUIPMENT

A. An oxygen source, face masks of different sizes, a bag-valve ventilation device, suction catheters, and suction source with canister and tubing.

B. Oral and nasopharyngeal airways (Fig. 1-2).

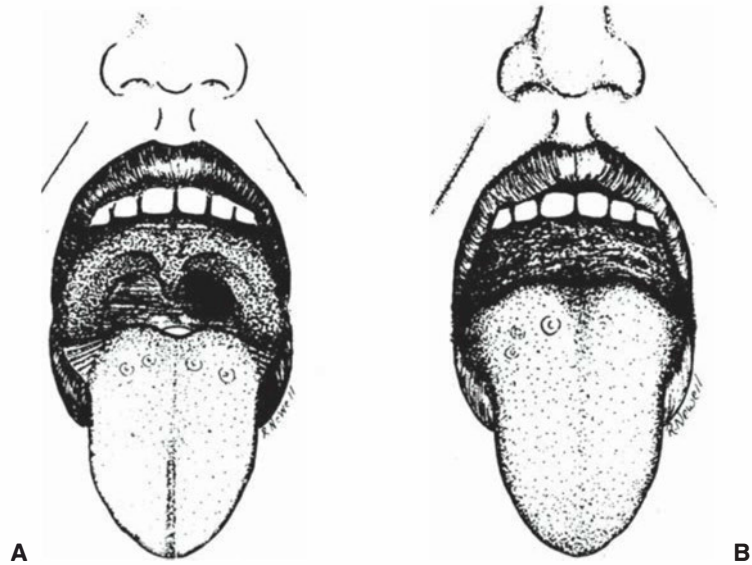

Figure 1-1. Mallampati classification: class I airway, faucial pillars, soft palate, and uvula can be visualized **(A)**; class II airway, faucial pillars, and soft palate can be visualized but the uvula is masked by the base of the tongue; and class III airway, only the soft palate can be visualized. The patient **(B)** has a class III airway, which is one of the predictors of difficult orotracheal intubation. (From Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J* 1985;32:420, with permission.)

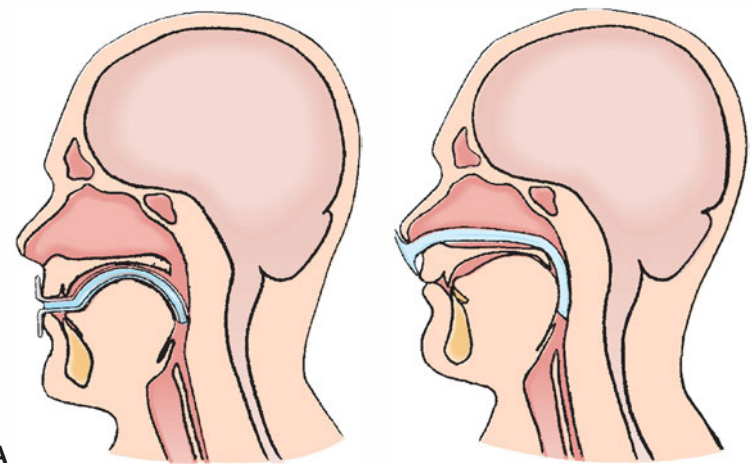

Figure 1-2. **A:** The proper position of the oropharyngeal airway. **B:** The proper position of the nasopharyngeal airway. (Reprinted Dorsch JA, Dorsch SE. *A practical approach to anesthesia equipment*. Philadelphia: Lippincott Williams & Wilkins, 2011:254–259, with permission.)

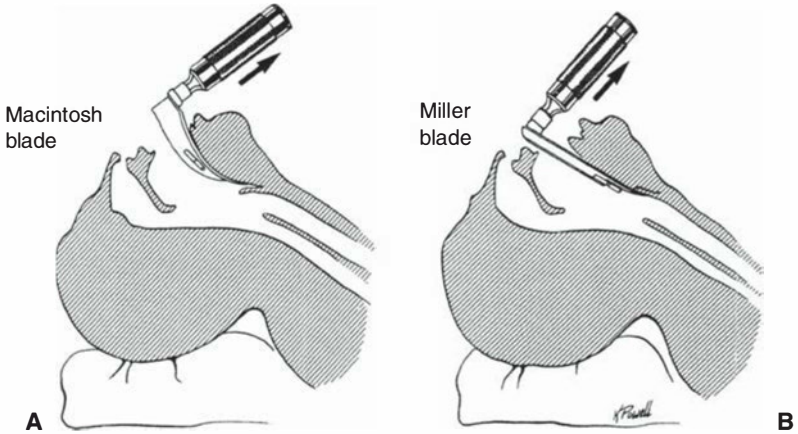

Figure 1-3. The two basic types of laryngoscope blades—Macintosh **(A)** and Miller **(B)**. The Macintosh blade is curved. The blade tip is placed in the vallecula, and the handle of the laryngoscope is pulled forward at a 45-degree angle. This maneuver allows visualization of the epiglottis. The Miller blade is straight. The tip is placed posterior to the epiglottis, thereby pinning the epiglottis between the base of the tongue and the straight laryngoscope blade. The motion on the laryngoscope handle is the same as that used with the Macintosh.

C. Laryngoscope blades and handle. Two basic types of laryngoscope blades are available: the curved blade (Macintosh) and the straight blade (Miller). The Miller blade is more useful in patients who have a cephalad and anterior laryngeal inlet (Fig. 1-3).

D. Various sizes of endotracheal tubes with stylets. In adults, endotracheal tubes with internal diameter of 7.0 to 8.0 mm are commonly used for women, while tubes with internal diameter of 8.0 to 9.0 mm are used for men.

E. A device to detect end-tidal carbon dioxide: capnograph.

F. Endotracheal tubes used in children may be based on this formula: Tube size (mm) = [16 + age (years)]/4.

G. Laryngeal mask airways (LMAs) can be used to provide a temporary airway until a more definite airway can be achieved. The LMA is contraindicated in patients at risk of aspiration due to the presence of a full stomach (Fig. 1-4).

V. AIRWAY OBSTRUCTION

A. The hallmark of upper airway obstruction is diminished or absent airflow in the presence of continued respiratory effort.

B. Airway obstruction can be complete or partial. Partial obstruction is recognized by noisy inspiratory sounds. Snoring is the sound of partial airway obstruction, which is most audible during expiration. Stridor suggests glottic obstruction and is heard most often in inspiration. Complete obstruction is an emergency with inaudible breath sounds.

Figure 1-4. Correct position of the LMA. (From Maltby JR, Loken RG, Watson NC, et al. The laryngeal mask airway: clinical appraisal in 250 patients. *Can J Anaesth* 1990;37:509, with permission.)

VI. TREATMENT

A. The head tilt is the simplest and first maneuver. The head is tilted back by placing one hand under the neck and pushing down on the forehead. This approach should not be used in patients with a fractured neck.

B. The second maneuver (jaw thrust) displaces the jaw forward by applying anterior pressure on the angle of the mandible. This procedure should not be done in patients with a dislocated or fractured jaw.

C. The triple airway maneuver (combination of head tilt, jaw thrust, and opening the mouth) is the most reliable manual method to establish airway patency.

D. When airway maneuvers are inadequate to establish airway patency, airway aids such as an oral or nasopharyngeal airway should be used (see Fig. 1-2).

E. Applying positive pressure that permits 20 cm H_2O to the airway throughout the respiratory cycle via the mask-bag-valve device can also be used to relieve the upper airway obstruction.

VII. OROTRACHEAL INTUBATION

A. Before we yield a patient unconscious, we have to ask the following four questions.

1. Can I ventilate this patient using a mask?

2. Will I be able to place a supraglottic device if needed?

3. Will I be able to intubate this patient?
4. If the surgical airway is required, will there be access to the patient's trachea?

B. Endotracheal intubation achieves four main goals: airway protection, providing upper airway patency, pulmonary hygiene, and allowing mechanical positive pressure ventilation.

C. The optimal position is the "sniffing" position: the head should be resting on a pad, which flexes the neck on the chest with concomitant extension of the head on the neck.

D. The laryngoscope handle is held in the left hand while the patient's mouth is opened as wide as possible. The laryngoscope blade is inserted into the right side of the mouth, the tongue is swept to the left, and the blade is advanced forward toward the base of the tongue.

E. The curved blade is advanced into the vallecula, and upward force at a 45-degree angle is used to raise the epiglottis. The straight blade is advanced, the tip of the blade is positioned beneath the epiglottis, and upward force is applied in the same manner as with the curved blade.

F. Once the glottic opening is visualized, the endotracheal tube is advanced through the vocal cords until the cuff just disappears. The cuff is inflated until moderate tension is felt in the pilot balloon cuff.

G. Determine that the tube is in the trachea. Signs of tracheal intubation consist of presence of CO_2 in the exhaled breath, breath sounds over the chest, lack of breath sounds over the stomach, lack of gastric distention, and respiratory gas moisture in the endotracheal tube.

H. Insertion of the tube to 23 cm at the incisors in males and 21 cm in females generally provides optimal endotracheal tube position.

I. If the laryngoscopist's view is not optimal, optimal external laryngeal manipulation (OELM) can be used by pressing the thyroid or cricoids cartilage, or hyoid bone in the cephalad and posterior direction.

J. In the unconscious patient who is considered to have a full stomach, cricoid pressure should be applied by using the thumb and forefinger together to push downward on the cricoid cartilage. This maneuver can prevent passive regurgitation of stomach contents into the trachea during intubation.

VIII. NASOTRACHEAL INTUBATION

A. The nasal approach generally provides the easier route for intubation.

B. Topical vasoconstrictors such as phenylephrine or cocaine (4%) should be applied to the nares to minimize nasal bleeding.

C. Nasotracheal intubation is contraindicated in basilar skull fractures and coagulopathies.

IX. FLEXIBLE ENDOSCOPY AND ALTERNATIVE TECHNIQUES OF AIRWAY MANAGEMENT

A. Fiberoptic endoscopy is useful in suspected spine injury, known or anticipated difficult airway, morbid obesity, and patients with high risk of aspiration (see Video 1-1).

B. It may be used in both awake and anesthetized patients via oral or nasal route.
C. It may be useful in critically ill patients to evaluate the endotracheal tube patency and position and to change endotracheal tubes in patients with difficult airways.
D. Fiberoptic endoscopy can be used with other intubation or alternative airway management techniques to overcome many difficult airways.
E. The LMA (see Fig. 1-4) or its variants and new generation supraglottic ventilatory devices are other alternative devices to manage the patient with a difficult airway. Rigid videolaryngoscopes that provide a non–line-of-sight view of the glottis are also available.
F. Needle cricothyrotomy and percutaneous dilatational tracheostomy can be done for emergent airway access.

X. COMPLICATIONS OF ENDOTRACHEAL INTUBATION

A. During intubation.

1. Laryngospasm.
2. Laceration.
3. Bruising of lips or tongue.
4. Damage to teeth.
5. Aspiration.
6. Endobronchial or esophageal intubation.
7. Perforation of oropharynx, trachea, or esophagus.
8. Epistaxis.

B. Postextubation.

1. Laryngospasm, sore throat, hoarseness, stridor, glottic or subglottic edema.
2. Long-term intubation may result in tracheal stenosis, tracheomalacia, and tracheal mucosal ulceration.

XI. EXTUBATION

A. Should be done in the patient who is fully awake and can protect his airway.
B. Oropharyngeal secretions should be suctioned, head of the bed should be elevated, and endotracheal tube should be removed after a cuff leak test.
C. In patients with a known difficult airway, extubation using an airway exchange catheter should be considered.
D. Supplemental oxygen should be provided, and the patient should be observed in a monitored setting.
E. Emergency airway equipment should be available to manage postextubation problems.

SUGGESTED READINGS

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2 Central Venous Catheters

Antonio Aponte-Feliciano, Alan Orquiola, Theofilos P. Matheos, and Stephen O. Heard

I. GENERAL PRINCIPLES

A. Catheter types.

1. Single lumen.
2. Multilumen (double, triple, or quad).
3. Introducer.
4. Double-lumen dialysis catheters.

B. Site selection.

1. Major sites.
   a. Internal jugular vein (IJV).
   b. Subclavian vein (SCV).
   c. External jugular vein (EJV).
   d. Femoral vein.
   e. Antecubital vein (peripherally inserted central catheters).
2. Depends on skill of operator: greater risk of pneumothorax with subclavian approach.
3. Risk of infection: femoral > internal jugular > subclavian.
4. Avoid sites involving infection, burns, or other dermatologic processes.

C. Methods to reduce risk of catheter infection.

1. Education program with safety checklist.
2. Empowering nursing to stop procedure if sterile technique is violated.
3. Dedicated catheter cart stocked with all necessary supplies.
4. Use chlorhexidine preparatory solution.
5. Use subclavian site preferably.
6. Use maximum barrier precautions: cap, mask, sterile gloves and gown, and sterile drape that entirely covers patient.
7. Remove catheters when no longer needed.
8. Avoid guidewire exchanges as possible.
9. Use antimicrobial impregnated catheters if infection rates remain high despite institution of infection control measures.
10. Avoid use of femoral site and move catheter from femoral site to another as soon as possible.

D. Use of ultrasonographic guidance.

1. Certain patient characteristics that carry higher risk of complications when using the anatomic approach.
   a. Anatomy: morbid obesity; local scarring; radiation therapy; short, thick neck; transplant patients; edema.

b. Comorbidities: coagulopathy, bullous emphysema, maximal ventilator support.

2. Allows better visualization of the anatomy, skin to vessel distance. Color flow Doppler allows one to identify flow direction (red toward and blue away from ultrasound probe) and avoidance of preexisting thrombus. The vein should be compressible.

3. The center of the screen will match the center of the probe. A mark on one side of the screen will match a mark or light on the ultrasound probe; this will allow orientation.

4. Decreases failure rate, multiple attempts at cannulation, mechanical failure rates, and infection rates.

5. Disadvantages: steep learning curve.

6. There are two ways to cannulate a vessel with ultrasound guidance.

a. Transverse view: provides complete visualization of the surroundings of the vessel. The needle should be inserted parallel to the probe; deviation could cause arterial puncture or structural damage.

b. Longitudinal plane: allows visualization of the path of the vessel and the needle entrance point. Ensure probe is maintained over the vein; sliding the probe laterally or medially could lead to an arterial puncture.

II. INDICATIONS

A. Monitoring of fluid status.
B. Administration of irritant medications or vasoactive substances.
C. Total parenteral nutrition.
D. Hemodialysis.
E. Placement of a temporary transvenous pacing wire.
F. Procurement of venous access when peripheral vein cannulation is not possible.
G. Aspiration of air in surgical procedures considered high risk for venous air embolism (e.g., posterior fossa craniotomy with the patient in the sitting position).
H. Venous access during cardiopulmonary resuscitation.

III. PROCEDURES

A. Universal protocol with a time-out must be followed.
B. IJV approach.

1. Approaches to IJV cannulation are the anterior, central, and posterior (Fig. 2-1).

2. Central (Fig. 2-1C).

a. The patient is placed in a 15-degree Trendelenburg position, and the head is turned to the contralateral side.

b. Using maximal barrier precautions, after infiltration of local anesthetic, the operator punctures the skin with a 22-gauge "finder" needle with an attached syringe at the apex of the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle (SCM) and the clavicle (base). The internal carotid artery pulsation is usually felt 1 to 2 cm medial to this point.

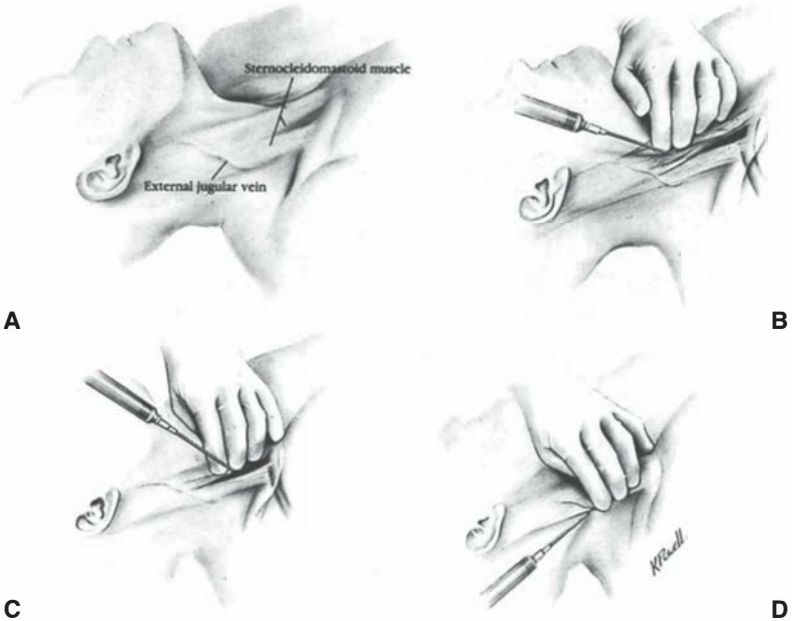

Figure 2-1. **A:** Surface anatomy. The IJV emerges from the base of the skull and enters the carotid sheath dorsally with the internal carotid artery, courses posterolaterally to the artery beneath the sternocleidomastoid muscle (SCM), lies medial to the anterior portion of the SCM in its upper part and beneath the triangle formed by the two heads of the muscle in the lower part, and enters the superior vena cava near the medial border of the anterior scalene muscle and beneath the sternal border of the clavicle. **B:** Anterior approach. **C:** Central approach. **D:** Posterior approach. To provide greater clarity of the anatomic landmarks, the sterile drape has been omitted from the figure.

c. The finder needle is directed at a 45-degree angle toward the ipsilateral nipple, while the operator applies constant aspiration on the syringe. After successful venipuncture with the finder needle, the large-bore needle is introduced in the identical plane. Once cannulation occurs, tubing (20 cm in length) can be attached to the needle to confirm a low-pressure system indicating an intravenous location.

d. After cannulation, the guidewire is then inserted through the large needle. Depth of insertion is limited to 15 to 20 cm to avoid arrhythmias.

e. A scalpel is used to make a larger skin incision (if needed). The bevel of the scalpel is against the guidewire, and the blade is facing away from the vessel. A dilator is advanced over the guidewire to dilate the tract and then removed. Care must be taken to hold the guidewire in place during dilator insertion to reduce the risk of vessel perforation. The central venous catheter (CVC) is then threaded over the guidewire.

3. Anterior approach (Fig. 2-1B). Initial needle insertion is 0.5 to 1 cm lateral to the carotid artery pulsation at the midpoint of the sternal head of the SCM.

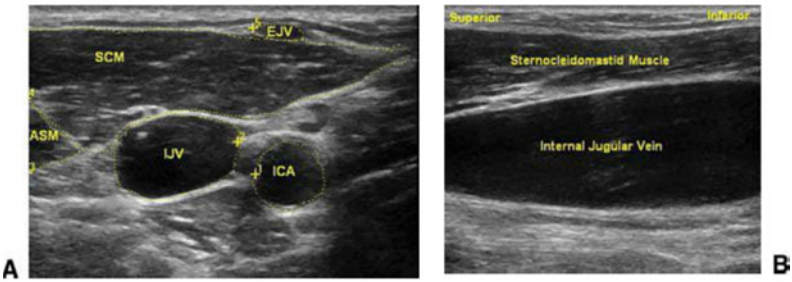

Figure 2-2. **A:** Transverse view of the IJV at the level of the cricothyroid membrane. SCM, sternocleidomastoid muscle; IJV, internal jugular vein; EJV, external jugular vein; ICA, internal carotid artery; ASM, anterior scalene muscle. Notice that the IJV is lateral to the ICA. **B:** Longitudinal view of the IJV.

4. Posterior approach (Fig. 2-1D).
   a. The EJV is the key landmark.
   b. The needle is inserted 1 cm dorsal to the point where the EJV crosses the posterior border of the SCM or 5 cm cephalad from the clavicle along the clavicular head of the SCM and is directed caudally and ventrally toward the suprasternal notch at an angle of 45 degrees from the sagittal plane and with a 15-degree upward angulation.
5. Ultrasound view (Fig. 2-2).

C. EJV approach.

1. The patient is positioned in a slight Trendelenburg position, with arms by the side and face turned to the contralateral side.
2. After sterile preparation, the venipuncture is performed with a 16-gauge catheter over the needle, using the operator's left index finger and thumb to distend and anchor the vein.
3. The needle is advanced in the axis of the vein at 20 degrees to the frontal plane. When free backflow of blood is established, the needle is advanced a few millimeters further, and the catheter is threaded into the vein over the needle.
4. A guidewire can be introduced through this catheter, and a CVC can be advanced over the guidewire.
5. Abduction of the ipsilateral arm and anteroposterior pressure exerted on the clavicle may help the guidewire to negotiate the angle formed at the junction of the EJV with the SCV.
6. The EJV can be successfully cannulated in 80% of patients.

D. Femoral vein approach.

1. The patient is positioned supine, the groin is prepared and draped, and the venipuncture is made 1 to 1.5 cm medial to the femoral arterial pulsation.
2. The femoral arterial pulsation is usually found at the junction of the medial and middle third of a line joining the anterior superior iliac spine and the pubic tubercle.

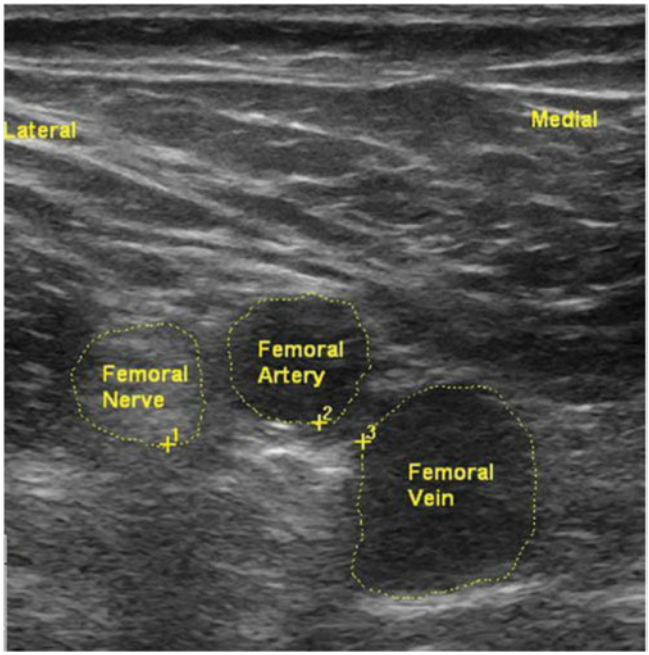

Figure 2-3. Transverse ultrasound view of the femoral vein anatomy. Structures from lateral to medial: femoral nerve, femoral artery, and the femoral vein.

3. An 18-gauge thin-walled needle attached to a syringe is inserted at a 45-degree angle pointing cephalad and 2 to 3 cm inferior to the inguinal ligament to minimize the risk of a retroperitoneal hematoma in the event of an arterial puncture.
4. Once venous blood return is established, the syringe is depressed to skin level, and free aspiration of blood is reconfirmed.
5. A guidewire and subsequently a dilator are advanced, and the catheter is finally threaded over the guidewire after the dilator has been removed.
6. Ultrasound view: The femoral anatomy can be appreciated in Figure 2-3.

E. SCV approach (Figs. 2-4 and 2-5).

1. The patient is positioned in a 15- to 30-degree Trendelenburg position, with a small bedroll between the scapulae.
2. The patient's head is turned to the contralateral side, and arms are by the side.
3. Infraclavicular approach.
   a. Skin puncture is made with an 18-gauge thin-walled needle attached to a syringe, 2 to 3 cm caudal to the midpoint of the clavicle and directed toward the suprasternal notch until it abuts the clavicle.
   b. The needle is "walked" down the clavicle until the inferior edge is cleared.
   c. As the needle is advanced, it is kept as close to the inferior edge of the clavicle as possible to avoid puncturing the dome of the pleura.

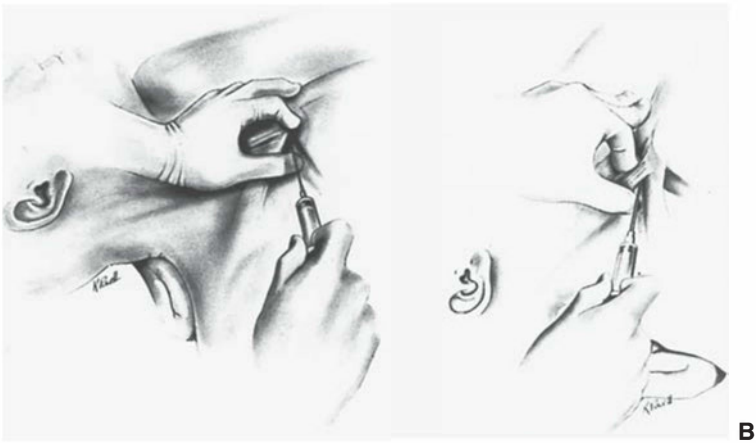

Figure 2-4. **A:** Patient positioning for subclavian cannulation. The SCV is a direct continuation of the axillary vein, beginning at the lateral border of the first rib and extending 3 to 4 cm along the undersurface of the clavicle to join the ipsilateral internal jugular vein behind the sternoclavicular articulation to become the brachiocephalic vein. The SCV is bordered by muscles anteriorly, the subclavian artery and brachial plexus posteriorly, and the first rib inferiorly. **B:** Cannulation technique for the supraclavicular approach. To provide greater clarity of the anatomic landmarks, the sterile drape has been omitted from the figure.

d. When blood return is established, the needle bevel (initially facing upward) is turned 90 degrees toward the heart, the syringe is removed, the guidewire is inserted, the needle is removed, and a dilator is advanced over the guidewire and removed.

e. The CVC is advanced over the guidewire to the appropriate depth.

4. Supraclavicular approach.
   a. The skin puncture is just superior to the clavicle and is lateral to the insertion of the clavicular head of the SCM.
   b. The needle is advanced toward the contralateral nipple, just under the clavicle, and it should enter the jugular subclavian at a depth of 1 to 4 cm.
   c. A 90% to 95% success rate can be achieved with this approach.
5. Ultrasound approach: Find the vessel lateral to the angle of the clavicle. Color Doppler can help with identification (see Fig. 2-5).

IV. POSTPROCEDURE CONSIDERATIONS

A. A chest radiograph is required to confirm proper position of the catheter and to ensure absence of a pneumothorax.

1. The tip of the catheter cannot be positioned in the right atrium or right ventricle because perforation of the cardiac wall may occur and cause tamponade.
2. Arrhythmias from mechanical irritation or vessel perforation may also result from catheter tip malposition. The caval atrial junction is

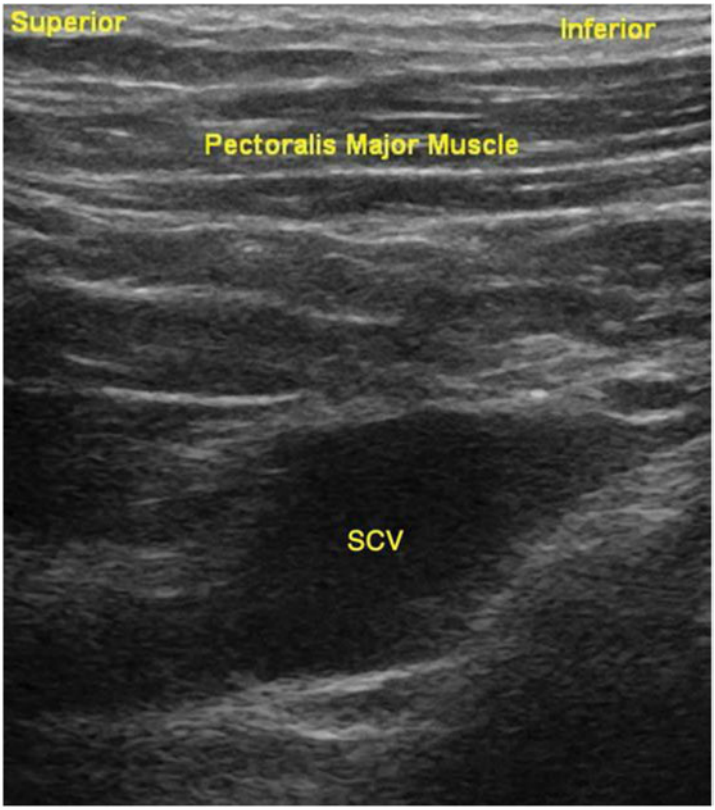

Figure 2-5. Subclavian vein, transverse view.

approximately 13 to 17 cm from the right-sided SCV or IJV insertion sites and 15 to 20 cm for left-sided insertions.

3. Application of a chlorhexidine-impregnated dressing will reduce the incidence of catheter-related bloodstream infection.

B. Other complications.

1. In addition to pneumothorax, cardiac tamponade, arrhythmias, and infection, observe for
   a. Air and catheter embolism.
   b. Hematoma.
   c. Arterial puncture.
   d. Hemothorax or hydrothorax.
   e. Line-associated thrombosis and/or embolism.

C. When removing a CVC, the patient should be positioned flat in the bed (i.e., head of the bed is not elevated) and an occlusive dressing applied to the insertion site after catheter removal to reduce the risk of venous air embolism.

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3 Arterial Line Placement and Care

Khaldoun Faris

I. GENERAL PRINCIPLES

A. Cannulation sites.

1. Radial artery.
2. Dorsalis pedis artery.
3. Brachial artery.
4. Femoral artery.
5. Axillary artery.

B. Anatomy.

1. The radial artery is one of two final branches of the brachial artery. It lies just lateral to the flexor carpi radialis at the wrist (Fig. 3-1). The anastomoses between the radial and ulnar arteries provide excellent collateral flow to the hand. A competent superficial or deep arch must be present to ensure adequate collateral flow.
2. The dorsalis pedis artery runs from the level of the ankle to the great toe. It lies superficially and just lateral to the tendon of the extensor hallucis longus.
3. The brachial artery lies in the antecubital fossa, medial to the tendon of the biceps, and in close proximity to the median nerve.
4. The common femoral artery courses under the inguinal ligament near the junction of the ligament's medial and middle thirds (Fig. 3-2).
5. The axillary artery begins at the lateral border of the first rib and ends at the inferior margin of the teres major muscle. The artery is mostly superficial and covered only by skin and fasciae.

C. Site selection.

1. The ideal artery should have extensive collateral circulation that will maintain the viability of distal tissues if thrombosis occurs.
2. The site should be comfortable for the patient, accessible for nursing care, and close to the monitoring equipment.
3. Sites involved by infection or disruption of the epidermal barrier should be avoided.
4. Larger arteries and catheters report pressures that are closer to aortic pressures. Distal artery recordings yield higher systolic values than central artery recordings, but the mean pressures are similar.

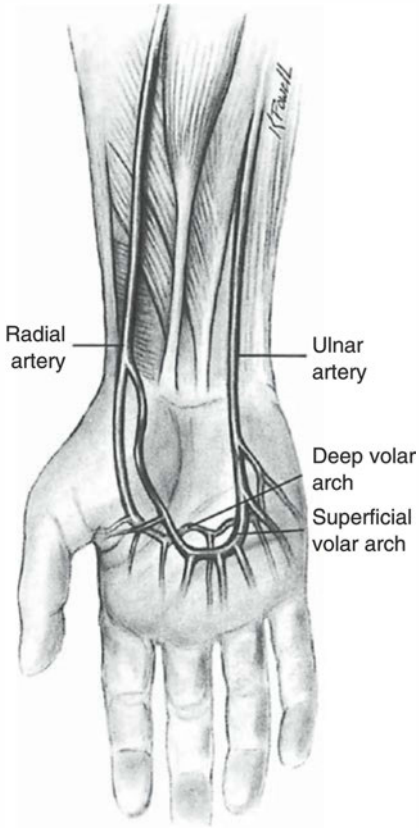

Figure 3-1. Anatomy of the radial artery. Note the collateral circulation to the ulnar artery through the deep volar arterial arch and dorsal arch.

II. INDICATIONS

A. Hemodynamic monitoring.

1. Beat-to-beat changes.
2. Waveform inspection.
3. The effect of arrhythmia on perfusion.
4. Continuous cardiac output (CO) monitoring using arterial pulse contour analysis.
5. Assessment of systolic pressure variation (SPV), pulse pressure variation (PPV), or stroke volume variation (SVV) to predict fluid responsiveness in mechanically ventilated patients with large tidal volumes (>8 mL/kg).

B. Frequent arterial blood gas sampling (more than two measurements per day).
C. Arterial administration of drugs such as thrombolytics.
D. Intra-aortic balloon pump use.

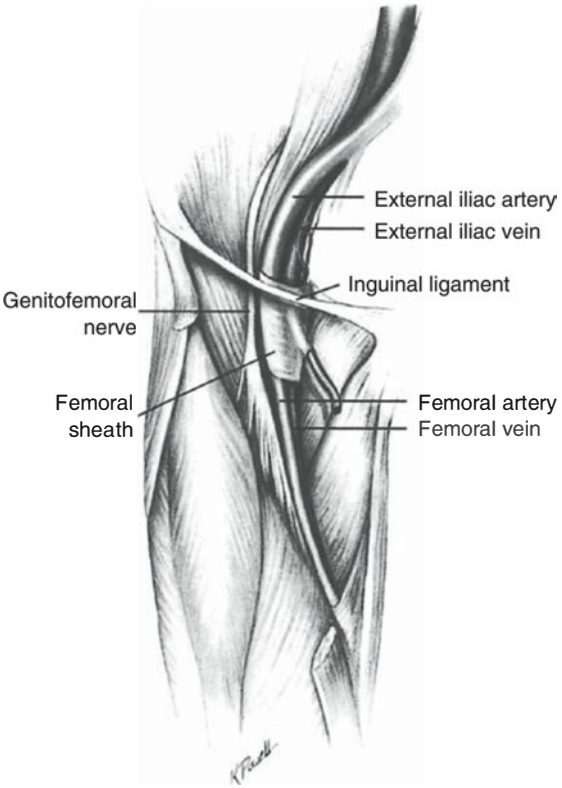

Figure 3-2. Anatomy of the right femoral artery and adjacent structures. The artery is cannulated below the inguinal ligament.

III. PROCEDURE

A. Equipment.

1. The equipment necessary to display and measure arterial waveform includes.
   - **a.** An appropriate intravascular catheter.
   - **b.** Fluid-filled noncompliant tubing with stopcocks.
   - **c.** A transducer.
   - **d.** A device for constantly flushing the line.
   - **e.** Electronic monitoring equipment.
2. Using this equipment, intravascular pressure changes are transmitted through the hydraulic (fluid-filled) elements to the transducer, which converts mechanical displacement into a proportional electrical signal. The signal is amplified, processed, and displayed as a waveform by the monitor.

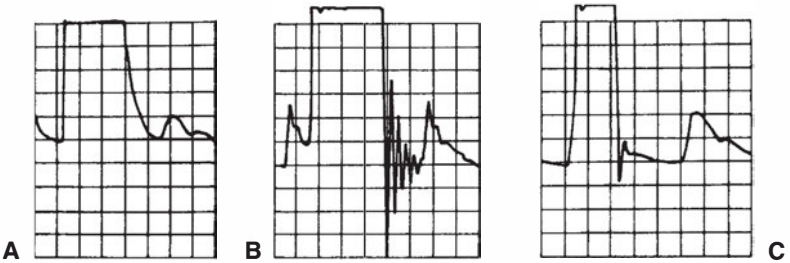

Figure 3-3. Fast-flush test. **A:** Overdamped system. **B:** Underdamped system. **C:** Optimal damping.

3. Sources of error.
   - **a.** Improper zeroing of the system and zero drift are important sources of error.
   - **b.** Calibration of the system is usually not necessary because of standardization of the disposable transducer.
   - **c.** If the zero referencing and calibration are correct, a fast-flush test will assess the system's dynamic response.
   - **d.** An optimal fast-flush test results in undershoot followed by small overshoot and then settles to the patient's waveform (Fig. 3-3).
   - **e.** Overdamped tracings are usually caused by air bubbles, kinks, clot formation, compliant tubing, loose connections, a deflated pressure bag, or anatomic factors. All these problems are usually correctable.
   - **f.** Underdamped tracings are caused by long tubing or an increased inotropic or chronotropic state.

B. Technique.

1. A time-out and the universal protocol must be followed. Foaming in and out, skin disinfection, and draping should be carried out as described in Chapter 2.
2. Radial artery cannulation.
   - **a.** Modified Allen test.
     - **i.** The modified Allen test does not necessarily predict the presence of collateral circulation, and some centers have abandoned its use as a routine screening procedure.
     - **ii.** To perform this test, the examiner compresses both radial and ulnar arteries and asks the patient to clench and unclench the fist repeatedly until pallor of the palm is produced. One artery is then released, and the time to blushing of the palm is noted. The procedure is repeated with the other artery.
     - **iii.** Normal palmar blushing is complete before 7 seconds (positive test), and a result of 15 or more seconds is abnormal (negative test).
   - **b.** Percutaneous insertion.
     - **i.** The hand is placed in 30 to 60 degrees of dorsiflexion. The volar aspect of the wrist is prepared and draped using the sterile technique, and lidocaine is infiltrated through a 25-gauge needle.

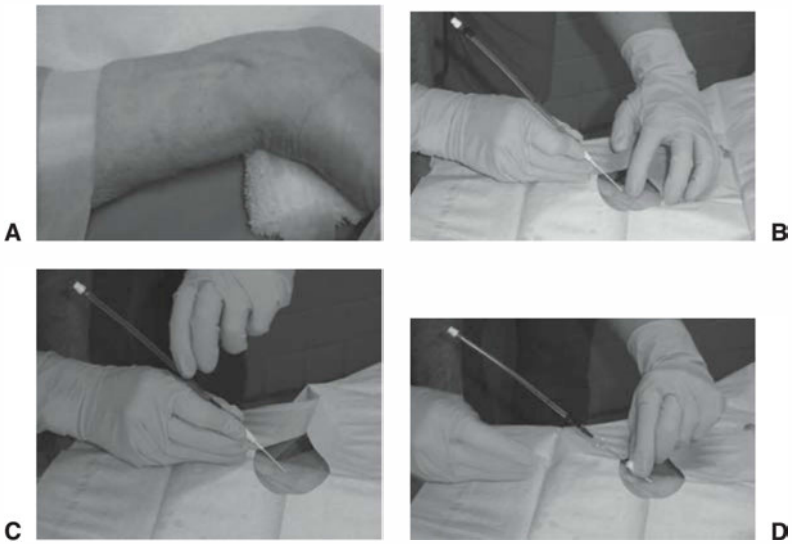

Figure 3-4. Cannulation of the radial artery. **A:** A towel is placed behind the wrist, and the hand is immobilized with tape. **B:** The 20-gauge catheter–needle–guidewire apparatus is inserted into the skin at 30- to 60-degree angle. **C:** The apparatus is advanced into the artery, and once a pulsatile flow is obtained, the guidewire is advanced. **D:** The catheter is advanced over the guidewire into the artery.

   ii. A 20-gauge catheter–needle–guidewire apparatus is used (Fig. 3-4). Entry is made at a 30- to 60-degree angle to the skin, approximately 3 cm proximal to the distal wrist crease.
   iii. The apparatus is advanced until arterial blood return is noted in the hub. The guidewire is passed through the needle into the artery to serve as a stent for subsequent catheter advancement.
   iv. The guidewire and needle are then removed, and placement is confirmed by pulsatile blood return.
   v. The cannula is attached to the transducer tubing and firmly secured, and the site is bandaged.
   vi. Video instruction for the insertion of a radial arterial line can be found at (http://www.nejm.org/doi/full/10.1056/NEJMvcm044149).

3. Dorsalis pedis artery cannulation.
   a. The patient's foot is placed in plantar flexion and prepared in the usual manner.
   b. Vessel entry is obtained approximately halfway up the dorsum of the foot.
   c. Advancement is the same as with cannulation of the radial artery.
   d. Systolic pressure readings are usually 5 to 20 mm Hg higher with dorsalis pedis catheters than with radial artery catheters, but mean pressure values are generally unchanged.

4. Brachial artery cannulation.
   a. Brachial artery cannulation is infrequently performed because of concern regarding the lack of effective collateral circulation.
   b. The median nerve lies in close proximity to the brachial artery in the antecubital fossa and may be punctured in 1% to 2% of cases.
   c. Cannulation of the brachial artery can be performed with the same apparatus as described for radial artery catheterization.
5. Femoral artery cannulation.
   a. The artery is cannulated using the Seldinger technique with one of several available prepackaged kits.
   b. The patient lies supine with the leg extended and slightly abducted.
   c. Skin puncture should be made a few centimeters caudal to the inguinal ligament to minimize the risk of retroperitoneal hematoma or bowel perforation.
   d. The needle is directed, bevel up, cephalad at a 45-degree angle. When arterial blood return is confirmed, the needle and syringe are brought down against the skin to facilitate guidewire passage.
   e. The guidewire is inserted, the needle is withdrawn, and a stab incision is made with a scalpel at the skin puncture site.
   f. The catheter is threaded over the guidewire to its hub, and the guidewire is withdrawn.
   g. The catheter is then connected to the transducer tubing and sutured securely to the skin.
6. Axillary artery cannulation.
   a. The patient's arm is abducted, externally rotated, and flexed at the elbow by having the patient place the hand under his or her head.
   b. The artery is palpated at the lower border of the pectoralis major muscle.
   c. The remainder of the catheterization proceeds as described for femoral artery cannulation.
7. Ultrasonographic-guided cannulation (see Chapter 22): Ultrasonography is used with increased frequency to guide vessel cannulation and minimize complications. Although it is mainly used in central venous cannulation, ultrasonography has been used to guide the cannulation of the femoral artery and less frequently the radial artery and other arteries.

IV. POSTPROCEDURE CONSIDERATIONS

A. Complications. The complications associated with arterial catheterization are listed in Table 3-1.

1. Thrombosis.
   a. Thrombosis is the single most common complication of intra-arterial catheters with an incidence of 5% to 25%.
   b. Symptomatic occlusion requiring surgical intervention occurs in <1% of cases.
   c. Most patients eventually recanalize, generally by 3 weeks after removal of the catheter.

TABLE 3-1 Complications Associated with Arterial Cannulation

Site	Complications
All sites	Pain and swelling
	Thrombosis
	Asymptomatic
	Symptomatic
	Embolization
	Hematoma
	Hemorrhage
	Limb ischemia
	Catheter-related infection
	Local
	Systemic
	Diagnostic blood loss
	Pseudoaneurysm
	Heparin-associated thrombocytopenia
Radial artery	Cerebral embolization
	Peripheral neuropathy
Femoral artery	Retroperitoneal hemorrhage
	Bowel perforation
	Arteriovenous fistula
Axillary artery	Cerebral embolization
	Brachial plexopathy
Brachial artery	Median nerve damage
	Cerebral embolization

d. If evidence of ischemia persists after catheter removal, thrombolytic therapy, radiologic or surgical embolectomy, and cervical sympathetic blockade are treatment options.

2. Cerebral embolization.

a. Factors that increase the risk for retrograde passage of air into the cerebral circulation are patient size and position (air travels up in a sitting patient), injection site, and flush rate.

b. The risk is minimized by clearing all air from tubing before flushing, opening the flush valve for no more than 2 to 3 seconds, and avoiding overaggressive manual flushing of the line.

3. Infection.

a. Infectious sequelae are the most important clinical complications associated with arterial cannulation.

b. Operators must wash their hands and wear sterile gloves during insertion of radial artery catheters, and triple barrier precautions are appropriate for large artery cannulations.

c. Nursing personnel should follow strict infection prevention guidelines when drawing blood samples or manipulating tubing.

d. Daily inspection of the site is mandatory, and the catheter should be removed promptly if signs of infection are noted.

e. It is no longer necessary to change arterial catheters routinely because studies of catheters remaining in place a week or longer have not demonstrated a higher rate of clinically important infection.

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4 Pulmonary Artery Catheters

Khaldoun Faris

I. GENERAL PRINCIPLES

A. Objectives.

1. Assess left ventricular (LV) or right ventricular (RV) function.
2. Monitor hemodynamic status.
3. Guide treatment with pharmacologic and nonpharmacologic agents.
4. Provide prognostic information.

B. Types.

1. Standard pulmonary artery catheter (PAC).
2. Pacing PAC.
3. Continuous cardiac output PAC.
4. Continuous mixed venous O_2 PAC.
5. RV ejection fraction PAC.

II. INDICATIONS

A. Cardiovascular disease.

1. Myocardial infarction, associated with cardiogenic shock, mechanical complications, or right heart failure.
2. Severe or progressive congestive heart failure.
3. Primary pulmonary hypertension for diagnosis and to guide vasodilator therapy.
4. Severe valvular heart disease.
5. Shock states.
6. Cardiac tamponade.

B. Perioperative period.

1. Cardiac surgery.
2. Aortic surgery.
3. Liver transplant.
4. Major abdominal and thoracic surgery in the setting of severe or unstable cardiac status.

C. Critical illness.

1. Major trauma and burns.
2. Severe sepsis and septic shock.
3. Acute renal failure.
4. Decompensated cirrhosis.

5. Acute respiratory distress syndrome (ARDS) with multiple organ dysfunction.
6. Severe head injury with refractory intracranial hypertension.
7. Cerebral vasospasm.
8. Severe preeclampsia/eclampsia.

III. PROCEDURE

A. Equipment.

1. The standard catheter length is 110 cm, and the most commonly used external diameters are 5 or 7 Fr.
2. A balloon is present 1 to 2 mm from the tip; when it is inflated with air, it guides the catheter from the greater intrathoracic veins through the right heart chambers into the pulmonary artery (PA).
3. The standard PAC used in the intensive care unit (ICU) is a quadruple-lumen catheter that has a lumen containing electrical leads for a thermistor positioned at the catheter surface, 4 cm proximal to its tip. The thermistor measures PA blood temperature and allows thermodilution cardiac output measurements.
4. A five-lumen catheter allows passage of a specially designed 2.4-Fr bipolar pacing electrode probe through the additional lumen for intracardiac pacing.
5. Continuous mixed venous oxygen saturation measurement is clinically available using a fiberoptic five-lumen PAC.
6. Continuous cardiac output can be measured by catheters equipped with a filament located in the RV portion of the catheter and a rapid response thermistor at the distal end. Pulse-heating currents are applied to the filament randomly, and temperature changes are detected by the thermistor.
7. Catheters equipped with fast-response (95 ms) thermistors allow determination of right ventricle ejection fraction (RVEF) and RV systolic time intervals.

B. Technique.

1. The insertion procedure of the standard PAC is discussed here. The insertion of the other types of PACs is beyond the scope of this chapter.
2. A time-out is performed to ensure "correct patient and side," and informed consent has been obtained if appropriate.
3. Central venous access using the appropriate size introducer sheath must first be obtained using sterile technique including maximum barrier precautions (see Chapter 2).
4. Continuous monitoring of the electrocardiogram (ECG) and pressure waveforms of the catheter is required, as well as equipment and supplies for cardiopulmonary resuscitation.
5. Flush all lumens of the catheter with normal saline.
6. Insert the catheter in the sterile sleeve adapter and pull the adapter proximally.
7. Pass the catheter through the introducer sheath into the vein and advance it, using the marks on the catheter shaft indicating 10-cm distances from the tip, until the tip is in the right atrium.

8. This maneuver requires advancement of approximately 35 to 40 cm from the left antecubital fossa, 10 to 15 cm from the internal jugular vein, 10 cm from the subclavian vein, and 35 to 40 cm from the femoral vein.
9. A right atrial waveform on the monitor with appropriate fluctuations accompanying respiratory changes or cough confirms proper intrathoracic location (Fig. 4-1).
10. With the catheter tip in the right atrium, inflate the balloon with the recommended amount of air.
    a. Inflation of the balloon should be associated with a slight feeling of resistance—if it is not, suspect balloon rupture and do not attempt further inflation or advancement of the catheter until balloon integrity has been properly reevaluated.
    b. If significant resistance to balloon inflation is encountered, suspect malposition of the catheter in a small vessel; withdraw the catheter and readvance it to a new position.
    c. Do not use liquids to inflate the balloon because they may be irretrievable and could prevent balloon deflation.
11. With the balloon inflated, advance the catheter until an RV pressure tracing is seen. Continue advancing the catheter until the diastolic pressure tracing rises above that observed in the RV (diastolic step-up), thereby indicating PA placement. Raising the head of the bed and tilting

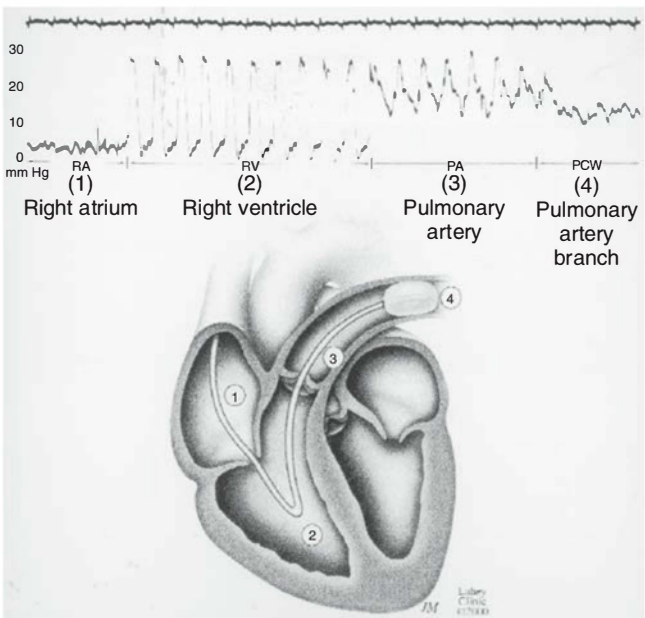

Figure 4-1. Pressure tracing recordings with corresponding locations as the PAC is passed into the occlusion position. PCW, pulmonary capillary wedge. (Reprinted from O'Donnell JM, Nacul FE. *Surgical intensive care medicine*. Norwell: Kluwer Academic Publishers, 2001:47, with permission.)

the patient to the right will facilitate passage of the catheter through the RV and reduce the risk of arrhythmias.

12. Advancement beyond the PA position results in a fall on the pressure tracing from the levels of systolic pressure noted in the RV and PA. When this is noted, record the pulmonary artery occlusion pressure (PAOP) and deflate the balloon.
13. Phasic PA pressure should reappear on the pressure tracing when the balloon is deflated. If it does not, pull back the catheter with the deflated balloon until the PA tracing appears.
    a. Carefully record the balloon inflation volume needed to change the PA pressure tracing to the PAOP tracing.
    b. If the inflation volume is significantly lower than the manufacturer's recommended volume or if subsequent PAOP determinations require decreasing balloon inflation volumes as compared with an initial appropriate volume, the catheter tip has migrated too far peripherally and should be pulled back immediately.
14. Most introducers have a valve that can be tightened to secure the catheter in the correct PA position. To avoid catheter kinkage, the valve should not be tightened too much.
15. Order a chest radiograph to confirm the catheter's position; the catheter tip should appear no more than 3 to 5 cm from the midline.
16. Fluoroscopic guidance by an experienced operator may be required to insert the PAC in certain disease states such as severe tricuspid regurgitation.

IV. POSTPROCEDURE CONSIDERATIONS

A. Pressure and waveform interpretation.

1. Normal resting right atrial pressure is 0 to 6 mm Hg.
2. The normal resting RV pressure is 17 to 30/0 to 6 mm Hg.
3. The RV systolic pressure should equal the PA systolic pressure (except in cases of pulmonic stenosis or RV outflow tract obstruction).
4. The RV diastolic pressure should equal the mean right atrial pressure when the tricuspid valve is open during diastole.
5. Normal resting PA pressure is 15 to 30/5 to 13 mm Hg with a normal mean pressure of 10 to 18 mm Hg.
6. The normal resting PAOP is 2 to 12 mm Hg and averages 2 to 7 mm Hg below the mean PA pressure.
7. Balloon occlusion may be confirmed by measuring an oxygen saturation of 95% or more from blood withdrawn from the distal lumen.
8. PAOP should be measured at end expiration because pleural pressure returns to baseline at the end of passive deflation.

B. Cardiac output measurement.

1. Most PACs are equipped with a thermistor 4 cm from the tip that allows calculation of cardiac output using the thermodilution principle.
2. In practice, a known amount of cold or room temperature solution (typically 10 mL of normal saline in adults and 5 mL of normal saline in children) is injected into the right atrium through the catheter's proximal port.

3. The thermistor allows recording of the baseline PA blood temperature and subsequent temperature change.
4. Cardiac output is inversely proportional to the integral of the time versus temperature curve.
5. Thermodilution cardiac output is inaccurate in low-output states, tricuspid regurgitation, and atrial or ventricular septal defects.

C. Derived parameters.

1. Cardiac index = CO (L/minute)/BSA (m^2).
2. Stroke volume = CO (L/minute)/heart rate (beats/minute).
3. Stroke index = CO (L/minute)/(heart rate [beats/minute] × BSA [m^2]).
4. Systemic vascular resistance (dyne/second/cm^{-5}) = ([mean arterial pressure – mean right atrial pressure (mm Hg)] × 80)/CO (L/minute).
5. Pulmonary arteriolar resistance (dyne/second/cm^{-5}) = ([mean PA pressure – PAOP (mm Hg)] × 80)/CO (L/minute).
6. Oxygen delivery (Do_2) (mL oxygen/minute/m^2) = cardiac index × arterial O_2 content.

D. Complications.

1. Balloon rupture.
2. Knotting.
3. Pulmonary infarction (peripheral migration of the catheter with persistent undetected wedging of the catheter).
4. PA perforation.
   a. Incidence is approximately 0.1% to 0.2%, although some postmortem series suggest that the true incidence of PA perforation is higher.
   b. Risk factors include pulmonary hypertension, mitral valve disease, advanced age, hypothermia, and anticoagulant therapy.
   c. Technical factors related to PA hemorrhage are distal placement or migration of the catheter, excessive catheter manipulation, use of stiffer catheter designs, and multiple overzealous or prolonged balloon inflations.
   d. PA perforation typically presents with hemoptysis.
   e. Emergency management for significant bleeding includes.
      i. Immediate wedge arteriography, intubation of the unaffected lung, and consideration of emergent embolization of the bleeding artery or emergency lobectomy or pneumonectomy.
      ii. PAC balloon tamponade resulted in rapid control of bleeding in one case report.
      iii. Application of positive end-expiratory pressure (PEEP) to intubated patients may also produce tamponade of hemorrhage caused by a PAC.
5. Thromboembolic complications.
6. Rhythm disturbances.
   a. Atrial and ventricular arrhythmias occur commonly during insertion of PACs.
   b. Patients with preexisting left bundle branch block are at risk of developing complete heart block during catheter insertion.
7. Intracardiac damage.
8. Catheter-related bloodstream infection and bacterial endocarditis.

E. Clinical use of PACs.

1. In unstable situations, PACs allow for direct and indirect measurement of several determinants of cardiac performance, thereby supplying additional data to aid in clinical decision making (Table 4-1). However, a number of recent well-conducted clinical studies have shown either no benefit or increased morbidity and mortality associated with their use. Furthermore, a study of normal volunteers showed that there was no correlation between CVP or PAOP and end-diastolic ventricular volume indexes and stroke volume index before and after volume infusion. Consequently, the use of PACs has decreased significantly in recent years.
2. A randomized trial conducted by the Canadian Critical Care Clinical Trials Group to compare goal-directed therapy guided by a PAC with standard care without the use of a PAC in elderly, high-risk surgical patients showed no improvement in mortality.
3. A multicenter randomized controlled trial conducted in France demonstrated that the use of PACs in the management of shock or ARDS, or both, albeit safe, does not improve mortality or morbidity.
4. A multicenter randomized controlled study conducted in the United Kingdom showed no clear evidence of benefit or harm by managing critically ill patients with a PAC.
5. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial concluded that adding the PAC to careful clinical assessment did not affect overall mortality or hospitalization in patients with severe symptomatic and recurrent heart failure.
6. The ARDS clinical trials network compared PAC-guided therapy in acute lung injury to central venous catheter (CVC)–guided therapy. The PAC-guided therapy did not improve survival or organ function but was associated with more complications.
7. In a retrospective analysis of the National Trauma Data Bank, the PAC was associated with survival benefit in the elderly and the severely injured in severe shock.
8. In a recently published study involving patients from five academic ICUs in Canada, Koo et al. observed a significant reduction in the utility of PACs over 5 years (2002–2006).

TABLE 4-1 Hemodynamic Parameters in Commonly Encountered Clinical Situations (Idealized)

	RA	RV	PA	PAWP	AO	CI	SVR	PVR
Normal	0–6	25/0–6	25/6–12	6–12	130/80	≥2.5	1,500	≤250
Hypovolemic shock	0–2	15–20/0–2	15–20/2–6	2–6	≤90/60	<2.0	>1,500	≤250
Cardiogenic shock	8	50/8	50/35	35	≤90/60	<2.0	>1,500	≤250
Septic shock	—	—	—	—	—	—	—	—
Early	0–2	20–25/0–2	20–25/0–6	0–6	≤90/60	≥2.5	<1,500	<250
Late[a]	0–4	25/4–10	25/4–10	4–10	≤90/60	<2.0	>1,500	>250
Acute massive pulmonary embolism	8–12	50/12	50/12–15	≤12	≤90/60	<2.0	>1,500	>450
Cardiac tamponade	12–18	25/12–18	25/12–18	12–18	≤90/60	<2.0	>1,500	≤250
AMI without LVF	0–6	25/0–6	25/12–18	≤18	140/90	≤2.5	1,500	≤250
AMI with LVF	0–6	30–40/0–6	30–40/18–25	>18	140/90	>2.0	>1,500	>250
Biventricular failure secondary to LVF	>6	50–60/>6	50–60/25	18–25	120/80	~2.0	>1,500	>250
RVF secondary to RVI	12–20	30/12–20	30/12	<12	≤90/60	<2.0	>1,500	>250
Cor pulmonale	>6	80/>6	80/35	<12	120/80	~2.0	>1,500	>400
Idiopathic pulmonary hypertension	0–6	80–100/0–6	80–100/40	<12	100/60	<2.0	>1,500	>500
Acute VSR[b]	6	60/6–8	60/35	30	≤90/60	<2.0	>1,500	>250

[a]Hemodynamic profile seen in approximately one-third of patients in late septic shock.
[b]Confirmed by appropriate RA–PA oxygen saturation step-up.
RA, right atrium; RV, right ventricle; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; AO, aortic; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; AMI, acute myocardial infarction; LVF, left ventricular failure; RVF, right ventricular failure; RVI, right ventricular infarction; VSR, ventricular septal rupture.
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5 Cardioversion and Defibrillation

Avani T. Mehta and Paulo J. Oliveira

I. GENERAL PRINCIPLES

A. Basic concepts.

1. Electric countershock.
   a. Delivering electrical energy to depolarize the myocardium to terminate a tachyarrhythmia.
   b. Definitions.
      i. **Cardioversion** delivers a *synchronized* shock, coinciding with the QRS complex on the electrocardiogram (ECG).
         (a) If countershocked during the "vulnerable" period, late ventricular systole marked by T wave on the ECG, there is risk of inducing ventricular fibrillation (VF).
         (b) Primarily used for emergency and elective treatment of various tachyarrhythmias.
      ii. **Defibrillation** delivers an *unsynchronized* shock to terminate VF and pulseless ventricular tachycardia (VT).
         (a) Because VF/pulseless VT is immediately life threatening and there is no well-defined QRS complex, an unsynchronized electrical countershock is delivered.
         (b) Defibrillation success is defined as termination of VF for at least 5 seconds following the shock, not by restoration of a perfusing rhythm.

B. Physiology of arrhythmias requiring cardioversion or defibrillation.

1. Reentry.
   a. Arrhythmias involving reentrant circuits (electrical activation over a closed conduction pathway) can be terminated with electric countershock.
      i. Examples include atrial fibrillation (AFib), atrial flutter, atrioventricular (AV) nodal reentrant tachycardia, and most VT and VF.
   b. Cardioversion and defibrillation disrupt reentry by depolarizing at least a threshold quantity of excitable tissue.
2. Increased automaticity.
   a. Arrhythmias involving increased impulse formation do not respond to electric countershock.
   b. Examples of unresponsive arrhythmias involving triggered activity are sinus tachycardia, focal atrial tachycardia, and some types of VT.

C. Mechanism of action.

1. Effective countershock silences an adequate portion of the myocardium through depolarization, while the remaining myocardium cannot perpetuate the arrhythmia.
2. Factors affecting successful shock include energy level, type of shock waveform, transthoracic impedance, and myocardial refractory state.
3. Subthreshold shocks may extinguish fibrillatory wavefronts, but often new wavefronts will form causing perpetuation of the fibrillation.

II. INDICATIONS

A. Urgent.

1. Hemodynamic instability.
2. Acute respiratory distress, congestive heart failure, and angina.
3. Important to recognize sinus tachycardia from rhythms that benefit from cardioversion or defibrillation.

B. Elective.

1. Absence of acute symptoms and signs.
2. Weigh risks and benefits.

III. PRECAUTIONS

A. Digitalis toxicity and electrolyte imbalance can increase the risk of inducing VT and VF.
B. Severe conduction disease (i.e., sick sinus syndrome) increases the risk of developing significant bradyarrhythmia after cardioversion.
C. Risk of thromboembolism in patients with AFib.

IV. PROCEDURE

A. Technical considerations.

1. Waveform types.
   a. Monophasic.
      i. Unipolar, delivers current in one direction.
      ii. Standard in older defibrillators.
      iii. Requires higher energy levels to terminate arrhythmia.
   b. Biphasic.
      i. Bipolar, delivers current in two directions with polarity reversal during the return phase.
      ii. Standard on most defibrillators.
      iii. Fewer shocks and lower total energy to terminate, with equal (perhaps superior) efficacy and improved safety profile.
2. Electrodes.
   a. Handheld paddles.
      i. Larger paddle size decreases transthoracic resistance, increasing energy delivery.
      ii. Pressure applied to chest with paddles decreases impedance and potentially improves efficacy of countershock.

iii. Current recommendations favor use of gel pads to decrease the risk of arcing and skin burns.

b. Self-adhesive pads.
   i. More common as convenient and easy to use.
   ii. Advantages: equally effective, no gel required, and minimizes risk to staff as less contact with bed and patient during delivery of shock.
   iii. May allow for temporary external pacing depending on model.

c. Anatomic placement.
   i. Minimize impedance by avoiding breast tissue and clipping excessive body hair.
   ii. Optimal placement (controversial).
      (a) Anterior–lateral: anterior pad/paddle on right infraclavicular chest and lateral pad/paddle lateral to the left chest longitudinally.
      (b) Anterior–posterior: anterior pad/paddle as above and posterior pad/paddle at left lower scapula.
         (1) This position may be favored for atrial tachyarrhythmias and in patients with implanted devices.
   iii. Biphasic waveform devices are less position dependent.

B. Patient preparation.

1. In unstable patients, perform countershock urgently.
2. If elective procedure, follow the below guidelines.
   a. NPO (*nil per os,* nothing by mouth) for 6 to 8 hours to decrease risk of aspiration.
   b. Obtain informed consent.
   c. Follow universal protocol.
   d. Constant heart rhythm monitoring and 12-lead ECG before and after countershock.
   e. Sedation medications with rapid onset of action and a short half-life: a benzodiazepine (midazolam) and/or a narcotic agent (fentanyl).
   f. Monitoring including frequent blood pressure and pulse oximetry checks; supplemental oxygen usually provided through nasal cannula.

C. Cardioversion procedure/using defibrillator.

1. If low-amplitude QRS, optimize detection by changing leads (essential in *synchronized* cardioversion).
2. Select "synchronization" function if performing cardioversion.
3. Select initial energy depending on device (most manufacturers will provide recommended energy dose on device) and arrhythmia.
   a. VF, pulseless VT: monophasic—360 J; biphasic—120 to 200 J.
   b. VT with pulse: monophasic—100 J; biphasic—unknown.
   c. AFib: monophasic—100 to 200 J; biphasic—100 to 120 J.
   d. Atrial flutter: monophasic—50 to 100 J; biphasic—unknown.
4. Charge capacitor, clear the area, and then deliver shock.
5. Be aware that many devices default back to "unsynchronized" mode following delivery of shock.
6. If no change in rhythm, escalate energy as appropriate and consider consulting a cardiologist or electrophysiology specialist.

D. Management of specific arrhythmias.

1. VF and pulseless VT.
   - **a.** Important changes in the advanced cardiac life support (ACLS) algorithm for VF/pulseless VT in the 2005 and 2010 guidelines published by the American Heart Association.
   - **b.** No longer recommend delivery of three "stacked" shocks; instead, deliver one shock followed by five cycles of cardiopulmonary resuscitation (CPR) before assessing rhythm.
   - **c.** Vasopressors (epinephrine or vasopressin) may be given before or after second shock, and antiarrhythmic agents (amiodarone is first line, but if unavailable, can consider lidocaine) may be considered before or after third shock.
   - **d.** Emphasis is placed on timely delivery of adequate, uninterrupted CPR between shocks.
   - **e.** CPR delivered in this manner (5 cycles of 30 compressions and 2 breaths per cycle or 2 minutes total) has been associated with improved success of defibrillation and potentially improved neurologic outcome.
2. AFib.
   - **a.** General overview.
     - **i.** Most common indication for cardioversion.
     - **ii.** Cardioversion performed in either the hemodynamically unstable patient or under elective circumstances to attempt reversion to normal sinus rhythm.
     - **iii.** Elective cardioversion for stable AFib may become less common.
     - **iv.** Published data have demonstrated that overall outcome may be more dependent on rate control and anticoagulation than on rhythm normalization.
   - **b.** Anticoagulation.
     - **i.** AFib/flutter is associated with development of thrombus in left atrial appendage or cavity during or after cardioversion.
     - **ii.** Risk of pericardioversion thromboembolism is 5.3% in patients not anticoagulated versus 0.8% in those who are anticoagulated.
     - **iii.** AFib of 24- to 48-hour duration is unlikely to be associated with thromboembolism.
     - **iv.** Two options in patients with atrial fibrillation of longer or indeterminate duration:
       - **(a)** Transesophageal echocardiogram (TEE).
         - **(1)** If no thrombus is noted in left atrial appendage, cardioversion may be safely performed.
         - **(2)** Anticoagulation with warfarin (goal international normalized ratio [INR] 2 to 3) should be provided for 4 weeks after cardioversion (time required for return of organized mechanical activity after cardioversion).
       - **(b)** Defer cardioversion until the patient has been anticoagulated at therapeutic range for 3 to 4 weeks.
         - **(1)** Must, again, anticoagulate for a minimum of 4 weeks after cardioversion.

V. POSTPROCEDURE CONSIDERATIONS

A. Complications.

1. Thermal burns to the chest—risk may be decreased with biphasic waveform devices (lower total energy required).
2. Risk of thromboembolic events, particularly when cardioverting AFib or flutter.
3. Countershocks can induce tachyarrhythmias and bradyarrhythmias.
4. Defibrillation in asystole should always be avoided because excessive vagal response may suppress intrinsic nodal activity.
   a. Always consider the possibility that VF with small-amplitude waves ("fine VF") may mimic asystole.
   b. Check more than one lead and for pulses before assuming a diagnosis of asystole.
5. Depolarizing the myocardium may inhibit the recovery of ventricular escape beat and thereby lead to worsening intrinsic pacemaker failure in individuals with baseline conduction abnormalities.
6. Clinically significant myocardial damage from cardioversion or defibrillation is unlikely; minimize the risk further by delivering shocks at least 1 minute apart.
7. Applying countershocks to patients with digoxin toxicity may be proarrhythmogenic, so check digoxin level and correct electrolytes before a procedure to minimize this risk.

B. Special circumstances.

1. Patients with implanted pacemakers and defibrillators.
   a. May undergo external cardioversion and defibrillation safely.
   b. External energy delivery may alter programming of internal device.
   c. Energy may also be conducted down an internal lead causing local myocardial injury or changing the devices functional thresholds.
   d. Never place pads/paddles directly over the internal device.
   e. Perform interrogation of device immediately after electric countershock delivery.
2. Cardioversion and defibrillation in pregnancy.
   a. Procedure has been performed in all trimesters without obvious fetal effects or induction of premature labor.
   b. Consider fetal heart rhythm monitoring during cardioversion.
3. Accidental hypothermia.
   a. Ventricular arrhythmias and asystole may be refractory to conventional therapy until the patient has been rewarmed.
   b. Cardiac arrest in this situation should be managed with an initial attempt at defibrillation and use of appropriate pharmacologic therapy.
   c. If unsuccessful, aggressive rewarming should continue and further attempts at defibrillation held until the core temperature reaches 30°C to 32°C.
   d. Optimal antiarrhythmic agent has not been determined.

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6 Pericardiocentesis

Dinesh Chandok† and Dennis A. Tighe

I. GENERAL PRINCIPLES

A. Pericardiocentesis is an important and potentially lifesaving procedure whereby a needle is inserted into the space between the visceral and parietal pericardium for the purpose of either sampling or draining pericardial contents (fluid, blood, pus, or gas).

B. Diagnostic versus therapeutic pericardiocentesis.

1. Diagnostic pericardiocentesis is performed to obtain small amounts of pericardial fluid for culture, cytologic study, or other fluid analyses.
2. Therapeutic pericardiocentesis is intended to drain fluid from the pericardial space to relieve pressure that limits diastolic filling.
3. Diagnostic and therapeutic pericardiocenteses are best performed electively, under controlled circumstances, with echocardiographic or fluoroscopic support.
4. Management of a patient with severe hemodynamic compromise may require that pericardiocentesis be performed on an emergency basis without imaging support.

C. Pericardial anatomy. Normally, only 15 to 50 mL of clear fluid is present in the pericardial space, its composition similar to that of plasma ultrafiltrate.

1. Visceral pericardium is composed of a single layer of mesothelial cells covering the myocardium and is loosely adherent to the underlying muscle by a network of blood vessels, lymphatics, and connective tissue.
2. Parietal pericardium is composed of a thick layer of fibrous connective tissue surrounding another mesothelial monolayer. This fibrous capsule is relatively nondistensible.

D. Diseases affecting the pericardium.

1. Several disease states may lead to inflammation of the pericardium or fluid accumulation including infections (viral, bacterial, fungal, parasitic), malignancies, certain rheumatologic disorders, uremia, myocardial infarction, recent cardiac surgery, and myocardial rupture.
2. The composition of the fluid may become exudative, purulent, or frankly bloody depending on the underlying cause.

E. Cardiac tamponade. Abrupt accumulation of fluid of 250 mL or less may lead to the clinical signs and symptoms of tamponade with equalization of pressures in all four cardiac chambers due to the relative noncompliance of the parietal pericardium. However, with slowly developing effusions, the

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parietal pericardium is able to stretch, and significantly larger amounts of fluid (sometimes >2 L) may accumulate without hemodynamic compromise. Three other clinical conditions promote hemodynamic compromise, even in the absence of large pericardial effusion: intravascular volume depletion, impaired ventricular systolic function, and ventricular hypertrophy with decreased elasticity of the myocardium (diastolic dysfunction).

II. PROCEDURE

A. General considerations.

1. In the patient with tamponade physiology, the treatment is drainage of the pericardial fluid. While awaiting performance of pericardiocentesis, some authors recommend medical treatment with volume infusion and, if needed, use of inotropic agents and vasoactive drugs. Medical treatment should be viewed as only a temporizing measure. It should be cautioned that aggressive fluid resuscitation may actually worsen the hemodynamic picture by intensifying the ventricular interactions and likely proves beneficial only to those patients who are hypovolemic. Administration of diuretics is contraindicated. Mechanical ventilation should be avoided if possible as it may further impair cardiac filling and output.
2. If time allows, a coagulation profile should be checked and corrected.
3. The authors recommend performing right heart catheterization whenever possible to measure pressures before and after pericardiocentesis.
4. Traumatic pericardial effusion, myocardial rupture, aortic dissection, and severe bleeding disorders are relative contraindications. No absolute contraindication to pericardiocentesis exists.

B. Material preparation.

1. *Site preparation*: 2% chlorhexidine gluconate and 70% isopropyl alcohol combination solution or equivalent (10% povidone–iodine solution is used only when there is a sensitivity to the chlorhexidine), large sterile drape, sterile gowns and gloves, masks, and caps; 1% lidocaine (without epinephrine), atropine, and code cart to bedside.
2. *Procedure*: a pericardiocentesis kit or an 18-gauge, 8-cm thin-walled needle with blunt tip; number 11 blade; multiple syringes (20 to 60 mL); ECG; hemostat; sterile alligator clip; specimen collection tubes; and pericardial drain if indicated.
3. *Postprocedure*: sterile gauze, dressings, and sutures.

C. Patient preparation.

1. The universal protocol should be followed, and maximum barrier precautions should be utilized.
2. The patient should be placed in a comfortable supine position with the head of the bed elevated to approximately 45 degrees or more.
3. The fully upright position may be necessary for extremely dyspneic patients. This position allows free-flowing effusions to collect inferiorly and anteriorly where they are most accessible through a subxiphoid approach.

D. Pericardiocentesis procedure.

1. Except under extreme emergency conditions, pericardiocentesis should be performed under imaging guidance. The primary imaging

modality used currently is bedside echocardiography to determine the location of the fluid, the presence of loculation, and the most accessible entry site (apical, parasternal, subxiphoid) into the pericardial space.

2. In general, the distance between the skin and the parietal pericardium using a subxiphoid approach is approximately 6.0 to 7.5 cm. This distance may be greater among obese patients or those with a protuberant abdomen.
3. The clinician should attach the needle to a 10-mL syringe, approximately half filled with 1% lidocaine. This technique permits delivery of anesthesia to the subcutaneous tissues and pericardium during needle entry while allowing sufficient space in the syringe for withdrawal of pericardial fluid.

E. Needle entry site selection.

1. The pericardial space may be entered at various points along the anterior thorax as guided by echocardiography, generally choosing the shortest distance between the skin and the fluid in the pericardial space. The subxiphoid approach is preferred in an emergency situation.
2. When considering the subxiphoid approach (the approach most commonly used by the authors), inspect and palpate to locate the xiphoid process and the left costal margin. The needle entry site should be 0.5 cm lateral to the left border of the xiphoid process and 1.0 cm inferior to the costal margin.
3. When using the parasternal approach, the needle insertion site should be perpendicular to the chest wall just lateral to the sternum in the fifth intercostal space.
4. With an apical approach, the needle insertion site should be located in the intercostal space below and 1 cm lateral to the cardiac apex.

F. Site preparation.

1. Strict sterile technique should be followed at all times. A wide area of the skin in the xiphoid region is prepared with a 2% chlorhexidine gluconate in 70% isopropyl alcohol combination solution (or equivalent), and the area is draped with a large fenestrated sterile drape.
2. The skin is anesthetized with 1% lidocaine without epinephrine.
3. A small skin incision is made at the entry site with a scalpel to facilitate the insertion of the blunt needle through the skin; the pericardiocentesis needle does not have a beveled edge to minimize the risk of myocardial puncture.

G. Needle insertion.

1. When passing through the skin from the subxiphoid approach, the angle of entry should be 45 degrees directing the needle superiorly aiming toward the patient's left shoulder.
2. Draw back on the plunger of the syringe while advancing the needle and before injecting the anesthetic agent.
3. The posterior edge of the bony thorax is usually only 1.0 to 2.5 cm below the skin, but this distance may be greater in obese patients. If the bony thorax is contacted during needle entry, reposition the needle so that it may be advanced under the costal margin.

4. Once the needle tip has passed beyond the posterior border of the bony thorax, the angle between the needle and the skin should be reduced to approximately 15 degrees. This angle of entry should be maintained while the needle is directed toward the left shoulder.
5. With the parasternal approach, the needle is guided by ultrasound toward the most prominent collection of fluid located closest to the chest wall.
6. When approaching from the apex, the needle should be aimed toward the patient's right shoulder.

H. Needle advancement.

1. Move the needle only in a straight trajectory from front to back. Moving the needle side to side may injure epicardial blood vessels and lymphatics.
2. Aspirate while advancing the needle. Pause to inject the subcutaneous tissues with lidocaine at periodic intervals.
3. A "give" will be felt on entry into the pericardial space and as fluid is aspirated.
4. Injection of agitated saline or perflutren lipid microspheres through the needle under echocardiographic guidance can ascertain if the needle tip is in the pericardial space or another structure if uncertainty about location exists.
5. A vasovagal response can occur when the pericardium is breached. Intravenous atropine or saline infusion may be required to reverse bradycardia and hypotension.
6. Observe the surface ECG monitor while advancing. The occurrence of frequent premature ventricular contractions and/or ST-segment elevations may indicate myocardial contact. In this situation, the needle should be withdrawn slightly and redirected.

I. Fluid evacuation. A large-volume pericardial effusion may be evacuated by attaching a 50-mL syringe to the pericardiocentesis needle with repeated aspirations. In general, we do not recommend this technique because manipulation of the needle during repeated attempts may cause trauma to the myocardium or frank rupture. The recommended approach is placement of a pericardial drain. To accomplish this, a multilumen pigtail-type catheter is introduced over a guidewire, as in the Seldinger technique, into the pericardial space and connected to a drainage bag.

J. Tamponade. If the procedure was performed to relieve tamponade, the patient's hemodynamic status should improve promptly. Such improvement may be observed after the evacuation of as little as 50 to 100 mL of fluid. Clinical signs that indicate relief of tamponade include an increase in systemic blood pressure and cardiac output with a concomitant fall in right atrial pressure and resolution of pulsus paradoxus.

III. POSTPROCEDURE CONSIDERATIONS

A. Monitoring. After pericardiocentesis, close monitoring is required to gauge the rate of pericardial effusion reaccumulation and the potential return of tamponade.

B. Chest radiograph. All patients should have an end-expiratory chest radiograph immediately following the procedure to detect the presence or document the absence of a pneumothorax.

C. A transthoracic echocardiogram should be obtained within several hours of the pericardiocentesis to confirm adequacy of pericardial drainage and at periodic intervals thereafter as indicated clinically.

D. Potential complications. Cardiac puncture with or without hemopericardium or myocardial infarction, pneumothorax, ventricular arrhythmias, bradycardia, injury to adjacent abdominal organs, cardiac arrest, coronary artery laceration, infection, fistula formation, and pulmonary edema.

E. Complications are most likely when the effusion is small (<250 mL), located posteriorly, or loculated or if the maximum anterior pericardial space is <10 mm as determined by echocardiography.

F. An unguided attempt at pericardiocentesis, as performed under emergency conditions, is associated with much higher complication rates.

G. Pericardial fluid samples should be sent to appropriate laboratories for analysis.

H. Diagnostic studies may include white blood cell count with differential; hematocrit; glucose, total protein, lactate dehydrogenase; Gram stain and culture for bacteria, fungi, and acid-fast bacilli; cytology; amylase; cholesterol; antinuclear antibody and rheumatoid factor; adenosine deaminase, total complement; C3; and rarely, in selected cases, specific viral or parasite studies.

I. Pericardial drain removal. The pericardial drain should be removed when the total output from it is <25 mL/day.

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7 Chest Tube Insertion and Care

Gustavo G. Angaramo

I. GENERAL PRINCIPLES.

Chest tube insertion involves the placement of a sterile tube into the pleural space to evacuate air or fluid into a closed collection system to restore negative intrathoracic pressure, promote lung expansion, and prevent lethal levels of pressure from developing in the thorax.

II. ANATOMY AND PHYSIOLOGY OF THE PLEURAL SPACE

A. The pleural space is a closed, serous sac surrounded by two separate layers capped by mesothelial cells, the parietal and visceral pleura. Normally there is a negative intrapleural pressure of 2 to 5 cm of water.

B. The pleural layers are in close apposition and, under normal physiologic conditions, allow free expansion of the lung in a lubricated environment.

III. INDICATIONS

A. Pneumothorax.

1. Accumulation of air in the pleural space is the most common indication for chest tube placement.
2. Diagnosis is often confirmed by chest radiography.
3. The risk of a recurrent ipsilateral spontaneous pneumothorax is as high as 50%, and the risk of recurrence after a second episode is 60% to 80%.

B. Hemothorax.

1. Accumulation of blood in the pleural space can be classified as spontaneous, iatrogenic, neoplastic, infectious, related to thromboembolism, or traumatic.

C. Empyema.

1. Empyemas are pyogenic infections of the pleural space that may result from
   - **a.** Necrotizing pneumonia.
   - **b.** Septic pulmonary emboli.
   - **c.** Spread of intra-abdominal infections.
   - **d.** Inadequate drainage of a traumatic hemothorax.

D. Pleural effusion.

1. Treatment of transudative pleural effusions is aimed at controlling the underlying cause. Tube thoracostomy is uncommonly indicated.
2. Exudative effusions, however, often require tube drainage depending on whether the fluid is free or loculated.

IV. CONTRAINDICATIONS

A. There are no absolute contraindications to chest tube insertion.

B. There are many *relative* contraindications.

1. Anticoagulation.
2. Prior ipsilateral thoracic surgery due to potential adhesions between the lung and the chest wall.
3. Extensive bullous lung disease.

V. PROCEDURE

A. Preparation.

1. Obtain a detailed informed consent.
2. Follow the universal precautions protocol.
3. Sterile technique including maximum barrier precautions is mandatory whether the procedure is performed in the operating room, the intensive care unit, or the emergency room.
4. Careful titration of analgesics or sedatives and injection of local anesthetic to provide optimal pain prevention and management.
5. Standard large-bore drainage tubes are made of either Silastic® or rubber.
   - **a.** Rubber tubes elicit more pleural inflammation, have fewer drainage holes, and are not easily identified on chest radiograph.
   - **b.** Silastic® chest tubes are either right angled or straight, have multiple holes, and contain a radiopaque stripe with a gap to mark the most proximal drainage holes.
   - **c.** Sizes are available from 6 to 40 Fr, with size selection dependent on the type of collection being drained.

B. Technique.

1. To properly insert a chest tube, the following steps are suggested:
   - **a.** Examine the chest imaging studies carefully.
   - **b.** Gather the necessary equipment.
     - **i.** Scalpel.
     - **ii.** Kelly clamps.
     - **iii.** Suture.
     - **iv.** Local anesthesia.
     - **v.** Needles.
     - **vi.** Syringes, dressings, tape, and a filled drainage apparatus (Pleurevac).
   - **c. Prepare the patient.**
     - **i.** Follow the universal precautions protocol. Position the patient with the operative side up, in the lateral decubitus position.
     - **ii.** Mark the fourth or fifth intercostal space in the anterior axillary line by landmarks (chest tubes are occasionally inserted anteriorly in the second intercostal space for pneumothoraces only!) (Fig. 7-1).
   - **d. Prepare and drape the surgical site.**
     - **i.** The area is prepared under sterile conditions with 4% chlorhexidine gluconate.
     - **ii.** The area is draped to include the ipsilateral nipple as a landmark.

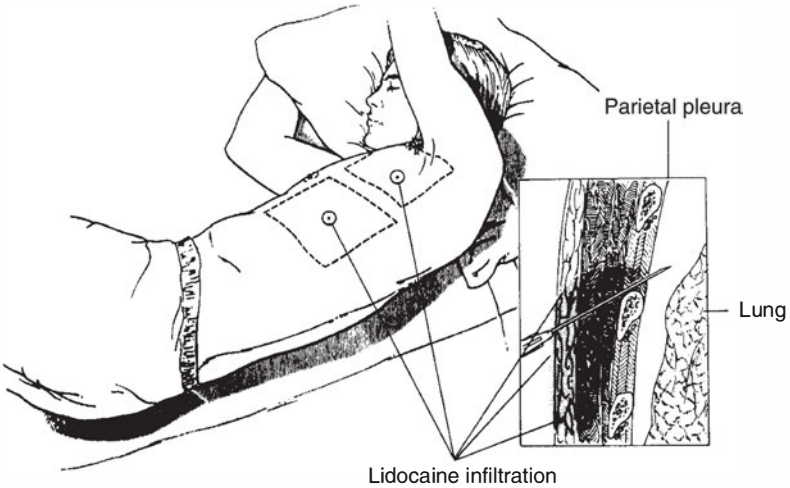

Figure 7-1. Proper patient positioning for chest tube insertion. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

e. Anesthetize the area.
- **i.** Include the skin over the incision site, periosteum above and below ribs, and the pleura.
- **ii.** Use 10 mL of 1% lidocaine, but have a full syringe in reserve if the patient needs supplementary medication during the procedure.
- **iii.** Tunnel the chest tube slightly to avoid air leak on removal. The actual entry point into the pleura will not be directly under the skin incision.

f. Make a skin incision.
- **i.** This should be no larger than the index finger (2 cm).

g. Make the subcutaneous tunnel.
- **i.** This should be done with ***spreading*** motions only using a Kelly clamp.
- **ii.** *Do not cut any tissue.* This will greatly decrease the chances of bleeding and will make a tract that will collapse on tube removal and seal off.
- **iii.** Spread along the interspace, going posteriorly for approximately 2 to 3 cm. This will place the tube in the posterior–superior direction, which will drain air and fluid properly.

h. Enter the pleural space.
- **i.** Using the tips of a Kelly clamp closed, holding the body of the clamp with two hands, and preventing uncontrolled entry and possible damage to underlying structures.
- **ii.** Once entered, spread the pleura with the tips of the clamp and do not insert the clamp into the chest (Fig. 7-2A).

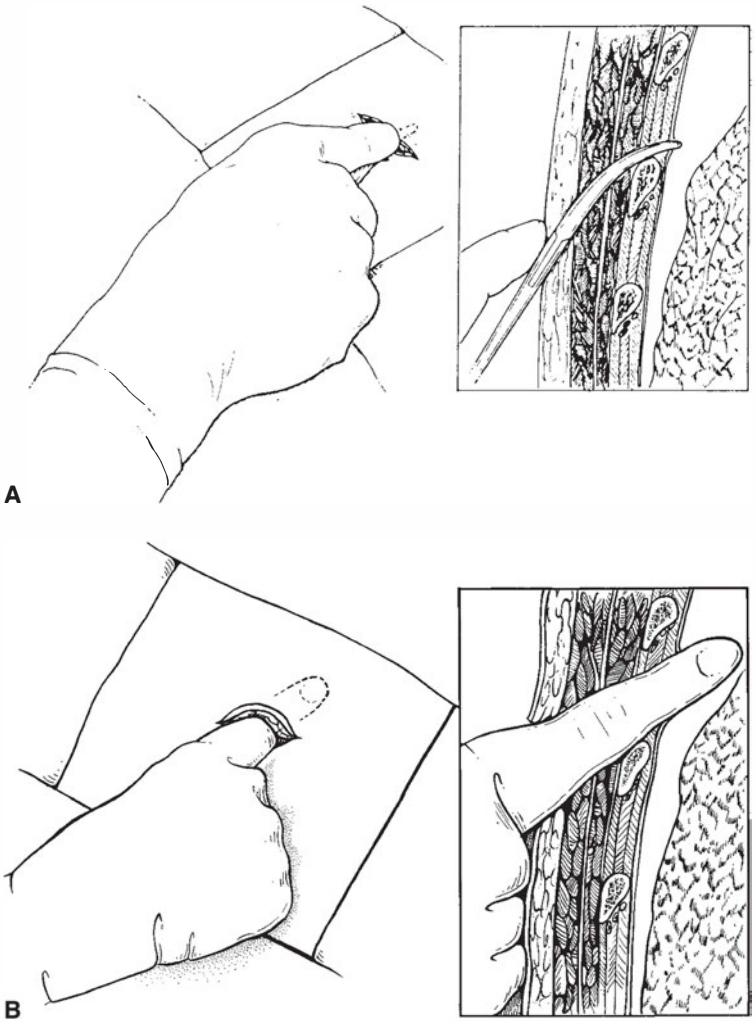

Figure 7-2. **A:** Enter the pleural space. **B:** Digitally explore the pleural space. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

i. Digitally explore the pleural space.

i. A finger is inserted into the pleural space to confirm proper location and a lack of pleural symphysis (Fig. 7-2B).

ii. If the space is not free and open, ***do not insert the tube***. Suture the skin incision. The lung will not collapse if the lung and pleura are adherent to the chest wall!

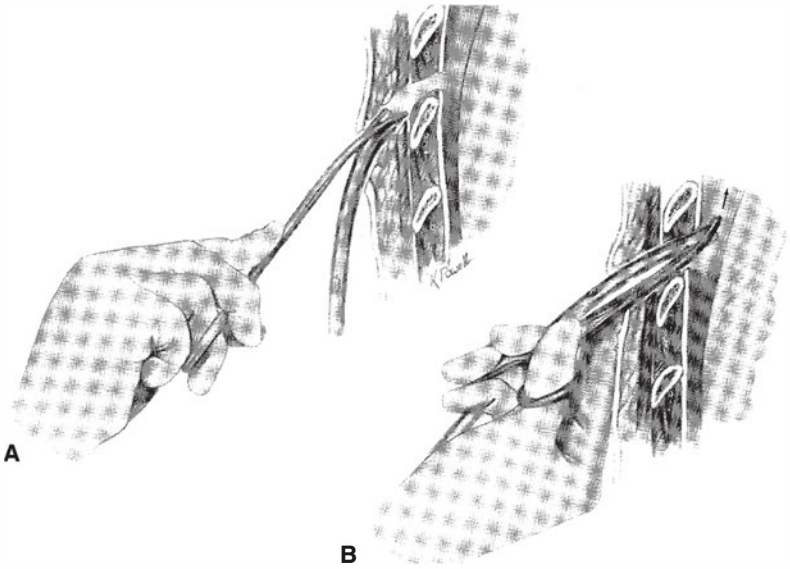

Figure 7-3. **A:** The end of the chest tube is grasped with a Kelly clamp and guided through the chest incision. **B:** The chest tube is oriented toward the apex. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

j. Insert the tube.
- **i.** The easiest way to do this is to have the tip of the tube clamped in the Kelly forceps.
- **ii.** Push the Kelly clamp and the tip of the chest tube into the pleural space, release the clamp, and continue inserting the tube.
- **iii.** Direct the tube posteriorly and superiorly (Fig. 7-3A and B).
- **iv.** The location of the tube should be confirmed by observing flow of air (seen as condensation within the tube) or fluid from the tube.
- **v.** Suture the tube to the skin to avoid slippage. *Be sure that all the holes are in the chest* (Fig. 7-4).

k. Connect to the Pleur-evac.
- **i.** *Do not evacuate more than 1,000 mL of fluid at a time.*
- **ii.** In a case of a massive hemothorax or effusion, allow the lung to reexpand for approximately 15 to 30 minutes before taking off another 1,000 mL maximum.
- **iii.** Reexpansion pulmonary edema (*ex vacuo*) is a real and potentially dangerous phenomenon.

l. Order a chest radiograph.

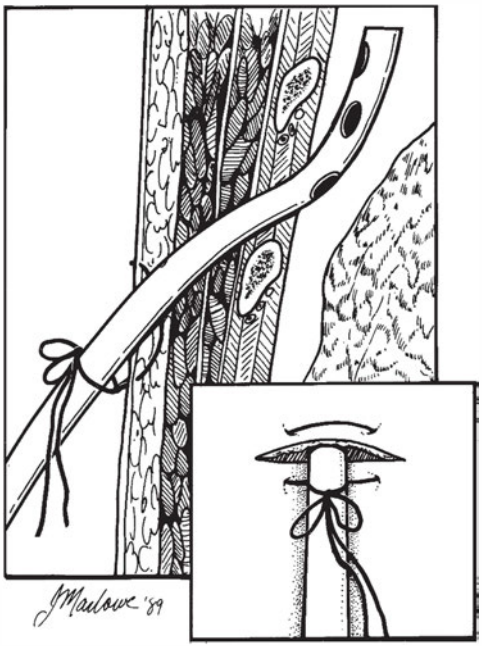

Figure 7-4. The tube is securely sutured to the skin with a silk suture. The suture is left long, wrapped around the tube. To seal the tunnel, the suture is tied when the tube is pulled out. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

VI. POSTPROCEDURE CONSIDERATIONS

A. Complications. Insertion is usually accompanied by a 1% to 2% incidence of complications, even when performed by experienced personnel.

1. Unintentional placement of the tube through the intercostal vessels or into the lung, heart, liver, or spleen can result in considerable morbidity and possible mortality.
2. Malposition of the tube has been detected up to 30% in critically ill patients.
3. Residual pneumothorax may follow removal of the tube as a result of a persistent air leak or due to entry of air through the tube site during or after removal.
4. Secondary infection of the pleural space following chest tube insertion is infrequent. Several investigations suggested benefit of prophylactic antibiotic regimens directed against *Staphylococcus aureus* only in patients undergoing tube thoracostomy in a trauma setting.

B. Chest tube management and care.

1. The tube and drainage system must be checked daily for adequate functioning.

2. Suction is routinely established at 15 to 20 cm H_2O.
3. Connection between the tube and the drainage system should be tightly fitted and securely taped.
4. Dressing changes should be performed every 2 to 3 days or as needed.
5. Serial chest radiographs should be obtained to evaluate the result of drainage.
6. Chest tubes can be pulled back but not *readvanced* into the pleural space, and if a tube needs to be replaced, it should always be at a different site.

C. Chest tube removal.

1. Indications for removal of chest tubes include
   a. Resolution of the pneumothorax, fluid accumulation in the pleural space, or both.
   b. For a pneumothorax, the drainage system is left on suction until the air leak stops. If an air leak persists, brief clamping of the chest tube can be performed to confirm that the leak is from the patient and not the system. When the leak has ceased for >24 to 48 hours (or if no fluctuation is seen in the seal chamber), the system is placed on water seal by disconnecting wall suction, followed by a chest film several hours later.
   c. If no pneumothorax is present and no air leak appears in the system with coughing and reestablishment of suction, the tube can be removed.
   d. For fluid collections, the tube can be removed when drainage is minimal.
2. Tube removal is often preceded by oral or parenteral analgesia.
3. As the patient takes deep breaths, the tube is removed and the hole is simultaneously covered with petrolatum gauze dressing at peak inspiration, at which point only positive pressure can be generated into the pleural space.
4. A chest x-ray is performed to check for a pneumothorax and is repeated 24 hours later to rule out accumulation of air or fluid.

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8 Bronchoscopy

Stephen J. Krinzman, Paulo J. Oliveira, and Richard S. Irwin

I. DIAGNOSTIC INDICATIONS

A. Hemoptysis.

1. To localize the bleeding site and diagnose its cause.
2. Greater sensitivity within 48 hours of time of active bleeding (34% to 91%) versus delayed (11% to 52%).
3. Rigid bronchoscopy preferred if massive hemoptysis to stabilize the airway.

B. Atelectasis. When chronic: to rule out endobronchial obstruction by malignancy or foreign body. When acute, mucus plugging is most common.

C. Diffuse parenchymal disease.

1. Transbronchial lung biopsy and bronchoalveolar lavage (BAL) can offer information about parenchymal processes. Highest yield in diagnosing sarcoidosis, lymphangitic carcinomatosis, or eosinophilic pneumonia.
2. Rarely provides definitive diagnosis for pulmonary vasculitis or to classify pulmonary fibrosis.
3. BAL is an aid for diagnosing opportunistic infections in the immunocompromised host.
4. Lung biopsy with fluoroscopy can improve localization and minimize pneumothorax risk.

D. Diagnosis of ventilator-associated pneumonia (VAP).

1. Threshold values: $>10^4$ colony forming units (cfu)/mL for BAL and $>10^3$ cfu/mL for protected specimen brush (PSB).
2. Performance characteristics.
   a. BAL: sensitivity 73%, specificity 82%.
   b. PSB: median sensitivity 67%, specificity 95%.
3. Blind telescoping catheters have similar performance.
4. Colony counts change rapidly within 12 hours of initiating antibiotic therapy; 50% of significant species drop to below diagnostic threshold.
5. Prospective randomized trials have not demonstrated improvement in mortality, intensive care unit (ICU) stay, or duration of mechanical ventilation with routine early bronchoscopy strategy.
6. Purulent secretions surging from distal bronchi during exhalation may be predictive of VAP.

E. Acute inhalation injury.

1. To identify the anatomic level and severity of injury after smoke inhalation.
2. Upper airway obstruction may develop within 24 hours of inhalation injury.
3. Acute respiratory failure is more likely with mucosal change at segmental or lower levels.

F. Blunt chest trauma. To rule out airway fracture after blunt trauma, suggested by hemoptysis, lobar atelectasis, pneumomediastinum, or pneumothorax.
G. Assessment of intubation-related trauma. To assess laryngeal or tracheal damage from endotracheal tubes.
H. Pulmonary infiltrates in immunocompromised patients.
   1. Diagnostic yield of BAL is 50% and leads to change of treatment in 17% to 38%.
   2. Transbronchial biopsy has small incremental yield, 7% to 12%, with significant complication rate. Yield may be higher in HIV patients.

II. THERAPEUTIC INDICATIONS

A. Excessive secretions/atelectasis.
   1. Lobar atelectasis not responding to chest physical therapy, incentive spirometry, and cough.
   2. Instillation of *N*-acetylcysteine (NAC), surfactant, and recombinant DNase have been utilized to help liquefy inspissated mucus. No clinical trials clearly support their routine use.
B. Foreign bodies.
   1. Rigid bronchoscopy is the procedure of choice to remove aspirated foreign bodies.
   2. Devices are available to help remove foreign bodies with the flexible scope.
C. Endotracheal intubation. Bronchoscope can be used as obturator allowing fiberoptically guided intubation.
D. Hemoptysis.
   1. Endobronchial tamponade can stabilize the patient to allow for more definitive therapy.
      a. Tamponade can be achieved with an inflated balloon–tipped catheter wedged in the lobar orifice.
   2. Massive hemoptysis can be controlled with iced saline lavage.
E. Central airway obstructing lesions. Consider laser photoresection or stenting of obstructing lesions of the larynx, trachea, and major bronchi.
F. Closure of bronchopleural fistula.
   1. To visualize a proximal or localize a more distal bronchopleural fistula.
   2. Materials injected through the bronchoscope may seal the fistula.
G. Percutaneous bedside tracheostomy. When routinely used, bronchoscopic visualization during the procedure significantly decreases the complications associated with this procedure.

III. COMPLICATIONS

A. When performed by a trained specialist, routine FB is extremely safe.
B. Mortality should not exceed 0.1%, and overall complication rate is <8.0%.

C. Death results from excessive premedication or topical anesthesia; respiratory arrest from hemorrhage, laryngospasm, or bronchospasm; and cardiac arrest from acute myocardial infarction.
D. Nonfatal complications: fever, pneumonia, vasovagal reactions, laryngospasm and bronchospasm, hypotension, cardiac arrhythmia, pneumothorax, anesthesia-related problems, and aphonia.
E. Critically ill patients have higher complication rates.
   1. Asthmatics: bronchospasm and laryngospasm.
   2. Bone marrow and stem cell transplant patients: major bleeding.
   3. Mechanically ventilated: Pneumothorax rate is 7% to 23% after transbronchial biopsy.

IV. CONTRAINDICATIONS

A. Coagulopathy in patients from whom biopsy specimens (brush or forceps) will be taken.
B. Unstable cardiac patients.
C. Untreated, symptomatic asthmatic patients (FB has been rarely used to relieve mucoid obstruction in intubated patients with status asthmaticus).
D. Severe, chronic obstructive pulmonary disease with associated hypercapnea (Premedication, sedation, and supplemental oxygen must be used with caution).
E. Elevated intracranial pressure (anesthetize using a combination of medications for cerebral protection, paralysis to prevent cough, and monitor to ensure adequate cerebral perfusion pressure).

V. PROCEDURAL CONSIDERATIONS

A. Preprocedural.
   1. Presence of underlying disease such as asthma, cardiovascular disease, uremia, and bleeding diathesis should be assessed.
   2. Antiplatelet drugs: One series found that aspirin does not increase risk of bleeding with transbronchial biopsy.
   3. Oxygenation: In critically ill, mechanically ventilated patients, bronchoscopy causes a drop in PaO_2 of 25% and up to 50% if ARDS.

B. Procedural.
   1. Lidocaine.
      a. Nebulized lidocaine is not effective.
      b. Instill 3 mL aliquots of 1% or 2% lidocaine to main carina and distal airways.
      c. Lidocaine is absorbed through mucous membranes, with similar serum levels to intravenous administration.
      d. Blood levels in the low therapeutic range are achieved if a total of <200 mg is used.
      e. Sudden change in mental status, hallucinations, seizures, increased sedation, or hypotension should suggest lidocaine toxicity.
      f. Methemoglobinemia has also been described with use of topical ester anesthetics. Use methylene blue to treat this complication.

2. Unintubated patients: transnasal or transoral passage of the bronchoscope.
3. Intubated patients.
   a. The bronchoscope is passed through a swivel adapter with a rubber diaphragm that prevents loss of the delivered tidal volume. Use a bite block to prevent damage to the bronchoscope.
   b. Consider the following before and during bronchoscopy.
      i. Endotracheal tube 8 mm or greater internal diameter allows for delivery of adequate tidal volume and safe passage of adult size bronchoscope. The risk of damage to the bronchoscope increases with smaller tubes.
      ii. Positive end-expiratory pressure (PEEP) of 20 cm H_2O may develop with bronchoscopy, with the risk of barotrauma.
      iii. PEEP already being delivered should be reduced or discontinued.
      iv. Inspired oxygen concentration must be increased to 100%.
      v. Expired volumes should be constantly measured; tidal volume usually has to be increased by 40% to 50%.
      vi. Suctioning will decrease delivered tidal volume and should be minimized.
4. During bronchoscopy, continuous oxygen therapy, oximetry, electrocardiography, and blood pressure monitoring are necessary.

C. Postprocedural.

1. Obtain a chest radiograph to rule out pneumothorax.
   a. After transbronchial biopsy in the nonintubated patient.
   b. After routine bronchoscopy in the intubated, mechanically ventilated patient.
      i. Return the ventilated patient to preprocedure ventilator settings.
      ii. In unintubated patients, supplemental oxygen is continued for 4 hours.
      iii. Monitor frequent vital signs until the patient is stable for at least 2 hours.

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9 Thoracentesis

Michael L. Barretti, Mark M. Wilson, and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Thoracentesis is the introduction of a needle, cannula, or trocar into the pleural space to remove accumulated fluid or air.

B. History (cough, dyspnea, or pleuritic chest pain) and examination (dullness to percussion, decreased breath sounds, and decreased tactile fremitus) suggest that an effusion is present. Chest radiograph (CXR) or ultrasonography (US) is essential to confirm the clinical suspicion.

C. Analysis of pleural fluid yields clinically useful information in >90% of cases.

D. The most common causes of pleural effusions are congestive heart failure, parapneumonic, malignancy, and postoperative sympathetic effusions.

II. INDICATIONS AND CONTRAINDICATIONS

A. Consider thoracentesis for pleural effusions in patients with pleurisy, who are febrile or are suspect for infection, whose clinical presentation is atypical for congestive heart failure, or whose course does not progress as anticipated.

B. Relative contraindications include those settings in which a complication from the procedure may prove catastrophic (i.e., known underlying bullous disease, the presence of positive end-expiratory pressure, a patient with only one functional lung).

C. Absolute contraindications include an uncooperative patient, the inability to identify the top of the rib at the planned puncture site clearly, operator inexperience with the procedure, and coagulopathy that cannot be corrected.

D. For pleural fluid present in only small quantity (less than half a hemidiaphragm obscured on an upright posterior–anterior [PA] CXR) or when the fluid is not freely flowing (i.e., loculated), directed guidance with dynamic (real-time) US or computed tomography is necessary to minimize the risk for serious complications.

III. PROCEDURE

A. Technique for needle-only or catheter-over-needle removal of freely flowing fluid.

1. Whenever available, US imaging of the thoracic cavity should be utilized (by qualified personnel) to identify the pleural fluid pocket as well as visceral structures both above and below the diaphragm.

2. If US is not available or the operator is inexperienced in chest sonography, obtain a lateral decubitus CXR to confirm a free-flowing pleural effusion.
3. Obtain informed written consent for the procedure and follow the universal precautions procedures.
4. Follow your institution-specific policy to ensure and document that you have the "correct patient, correct procedure, correct site."
5. With the patient sitting, arms at side, mark the inferior tip of the scapula on the side to be tapped. This approximates the eighth intercostal space, the lowest level that may be safely punctured unless US determines a lower interspace can safely be entered.
6. Position the patient sitting at the edge of the bed, leaning forward over a pillow-draped bedside table, with arms crossed in front to elevate and spread the scapulae. An assistant should stand in front of the table to prevent any unexpected movements.
7. Percuss the patient's posterior chest for the highest point of the effusion. The interspace below this should be entered in the posterior axillary line. Mark the superior aspect of the rib with your fingernail (the inferior border of each rib contains an intercostal artery and should be avoided).
8. Using sterile technique, cleanse and drape the area surrounding the puncture site.
9. Anesthetize the superficial skin with 2% lidocaine using a 25-gauge needle. Use an 18- to 22-gauge needle to anesthetize the deeper soft tissues, aiming for the top of the rib. Always aspirate as the needle is advanced and before instilling lidocaine to ensure that the needle is not in a vessel or the pleural space. Fluid enters the syringe on reaching the pleural space. The patient may experience discomfort as the needle penetrates the well-innervated parietal pleura. Be careful not to instill anesthetic into the pleural space; it is bactericidal for most organisms, including *Mycobacterium tuberculosis*.
   a. **Diagnostic thoracentesis (30 to 50 mL):** Insert the catheter-over-needle apparatus (or 20-gauge, 1.5-in. needle attached to a three-way stopcock and 50-mL syringe) along the anesthetic tract, always aspirating through the syringe as the needle is slowly advanced. Once pleural fluid returns using the needle-only technique, stabilize the needle by attaching a clamp to the needle where it exits the skin to prevent further advancement of the needle into the pleural space. Once pleural fluid is obtained using the catheter-over-needle technique, direct the apparatus downward to ensure that the catheter descends to the most dependent area of the pleural space. Advance the catheter forward in a single smooth motion as the inner needle is simultaneously withdrawn.
   b. **Therapeutic thoracentesis (>100 mL):** involves placement of a catheter into the pleural space, similar to above. Commercial kits are widely available, each with specific instructions. Operators should be thoroughly familiar with the recommended procedure and should receive appropriate supervision from an experienced operator before performing therapeutic thoracentesis on their own.

10. Fill a heparinized blood gas syringe with pleural fluid from the side port of the three-way stopcock, express all air from the sample, cap it, and place it in a bag containing iced slush for immediate transport to the laboratory. Fill the 50-mL syringe and transfer its contents into appropriate containers for planned analyses. Always maintain a closed system during the procedure to prevent room air from entering the pleural space.
11. With thoracentesis completed, remove the needle (or catheter) from the patient's chest. Apply pressure to the wound for several minutes, and apply a sterile bandage.
12. Obtain a postprocedure upright end-expiratory CXR if a pneumothorax is suspected. Immediately after the procedure, draw venous blood for total protein and lactate dehydrogenase (LDH) determinations. These studies are necessary to interpret pleural fluid values.

B. Technique for removal of freely moving pneumothorax.

1. Follow the same general protocol described earlier for catheter-over-needle removal of freely flowing fluid but instead, position the patient supine with the head of the bed elevated 30 to 45 degrees.
2. Prepare the anterior second or third intercostal space in the midclavicular line (to avoid the more medial internal mammary artery).
3. Have the bevel of the catheter-over-needle apparatus facing upward and direct the needle superiorly to guide the catheter into the superior aspect of the hemithorax.
4. Air may be actively withdrawn by syringe or pushed out when intrapleural pressure is supraatmospheric (e.g., during a cough), as long as the catheter is intermittently open to the atmosphere. Air can leave but not reenter the pleural space if a one-way (Heimlich) valve system is attached or if the catheter is put to underwater seal.
5. If a tension pneumothorax is known or suspected and a chest tube is not readily available, quickly insert a 14-gauge angiocatheter according to the foregoing technique. If a tension pneumothorax is present, air will escape under pressure. When the situation has been stabilized, replace the catheter with a sterile chest tube.

IV. POSTPROCEDURE CONSIDERATIONS

A. The overall complication rate from thoracentesis is ≤5% when done by experienced intensivists but may reach 50% to 78% when performed by less experienced operators.

B. Major, possibly life-threatening, complications may occur in 15% to 19% and include pneumothorax, hemorrhage, hypotension, reexpansion pulmonary edema, and venous or cerebral air embolism (rare).

C. The risk of pneumothorax varies depending on baseline patient characteristics (e.g., presence or absence of chronic obstructive pulmonary disease), operator experience, and the method used to perform the procedure.

D. Minor complications depend on the method used and occur in 16% to 63%, including dry tap, anxiety, dyspnea, cough, pain, and subcutaneous hematoma or seroma.

V. INTERPRETATION OF PLEURAL FLUID ANALYSIS

A. A transudate is biochemically defined by meeting *all* the following (Light) criteria: pleural fluid-to-serum ratio for total protein <0.5, pleural fluid-to-serum ratio for LDH <0.6, and an absolute pleural fluid LDH less than two-thirds the upper limits of normal of the serum LDH. Alternative diagnostic criteria also exist with similar accuracy, sensitivity, and specificity values compared with Light criteria. If a transudate is present, then generally no further tests on pleural fluid are generally indicated.

B. An exudate is present when any of the criteria for transudate are not met. Further evaluation is usually warranted.

1. A pleural fluid pH <7.20 narrows the differential diagnosis to systemic acidemia, empyema or parapneumonic effusion, malignancy, rheumatoid or lupus effusion, extrapulmonary tuberculosis, ruptured esophagus, or urinothorax. These effusions may potentially require consideration for chest tube drainage.
2. Pleural fluid glucose levels <50% of the serum level may be found with empyema, malignancy, rheumatoid or lupus effusion, extrapulmonary tuberculosis, or ruptured esophagus.
3. Although not diagnostic, pleural fluid white blood cell counts exceeding 50,000/mm^3 strongly suggest bacterial pneumonia or empyema but may also be seen in effusions associated with rheumatoid arthritis. Pleural fluid lymphocytosis, when present in >80% of cells, suggests tuberculosis or malignancy.
4. Grossly bloody effusions contain >100,000 cells/mm^3 and are most commonly seen in trauma, malignancy, or pulmonary infarction. Hemothorax is defined by a pleural fluid hematocrit of 50% or greater of the serum hematocrit.
5. Chylous pleural effusions are defined by triglyceride levels >110 mg/dL and may be seen with trauma involving the thoracic duct, malignancy (especially lymphoma), and in patients with advanced liver disease.
6. If initial cytologic results are negative for malignancy and a strong clinical suspicion exists, additional pleural fluid samples can increase the chance of a positive result. The addition of a pleural biopsy increases the yield to a modest amount over cytology on two separate specimens. Cytologic examination may also definitively diagnose rheumatoid pleuritis.

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10 Tracheostomy

Mark L. Shapiro and Vanessa Schroder

I. GENERAL PRINCIPLES

A. Benefits.

1. Improved patient comfort, decreased sedation requirements, and decreased work of breathing are thought to translate into improved ability to wean from the ventilator.
2. Tracheostomies provide the possibility for vocal communication in intermittently ventilated patients as well as allow for improved oral hygiene.
3. Reduced risk of laryngeal injury from prolonged endotracheal (ET) intubation.

B. Tracheostomies do not necessarily improve outcomes.

1. Performing "early" tracheostomy (<7 days) may improve some short-term outcomes but at the risk of some procedure-related complications. Early tracheostomies have not been shown to improve long-term outcomes when compared to tracheostomies performed later in the hospital course (around 7 to 14 days).
2. Tracheostomies are not clearly associated with increased rates of intensive care unit (ICU) or hospital survival or a decrease in the frequency of aspiration or nosocomial pneumonia.

C. There are currently a variety of techniques available for tracheostomy creation.

1. Surgical/open.
2. Percutaneous.
3. Semiopen.

D. These techniques allow for the procedure to be safely performed in a range of patient care settings by both surgeons and nonsurgeon practitioners.

1. Emergency department.
2. ICU.
3. Operating room.

II. ANATOMY OF THE TRACHEA

A. The trachea occupies the neck and thorax immediately anterior to the esophagus as the distal continuation of the larynx.

B. It terminates at the carina or bifurcation (located at the level of the seventh thoracic vertebra) where it divides into the right and left main bronchi and subsequently into the lobar bronchi.

C. Rings.
   1. The thyroid cartilage is the most superior cartilage and is easily palpable.
   2. The cricoid cartilage is the only continuous ring of the trachea.
   3. Between the thyroid and cricoid cartilages is a palpable indentation corresponding to the cricothyroid membrane. This is the site of access to the trachea during an emergent cricothyroidotomy.
   4. Accepted site for tracheotomy is the second or third tracheal ring.

D. Special considerations in children.
   1. The trachea is much shorter in children than in adults.
   2. In children under the age of 9, tracheostomy rather than cricothyroidotomy is the procedure of choice in an emergency.

III. INDICATIONS

A. Airway obstruction secondary to thyroid tumors, pharyngeal abscess, or granulation tissue from prolonged intubation or tracheal irritation or severe inflammation due to asthma, trauma, or anaphylaxis.
B. Need for prolonged mechanical ventilation (median 11 days in a multicenter trial) in the setting of head injury, severe chronic obstructive pulmonary disease (COPD), quadriplegia, and high spinal cord injuries.
C. As an airway control strategy for patients undergoing facial or esophageal reconstruction.

IV. GENERAL PROCEDURAL CONSIDERATIONS AND RELATIVE CONTRAINDICATIONS

A. In the elective setting, it is important to ensure that the patient is not clinically coagulopathic due to either liver disease or medications.
B. Obese patients require a larger incision and a longer cannula and may benefit from a procedure performed in the operating room where factors such as lighting and positioning may be more carefully controlled.
C. Caution should be used in patients with high positive end-expiratory pressure (PEEP) requirements (>10 cm H_2O) as during the procedure patients may experience alveolar derecruitment leading to hypoxemia and acute lung injury.
D. Subcutaneous and mediastinal emphysema are not contraindications to tracheostomy.
E. Patients with closed head injury and an elevated intracranial pressure (ICP) may not be appropriate for tracheostomy until the ICP is controlled. Percutaneous tracheostomy is particularly contraindicated as elevated $PaCO_2$ during bronchoscopy may further increase ICP.
F. Necks distorted by tumors, hematoma, or previous radical neck surgery.
G. An enlarged thyroid can be a source of uncontrolled bleeding and poor visualization.
H. A high-riding innominate artery especially in patients with large necks is a rare but important source of potential life-threatening bleeding.

V. OPEN TRACHEOSTOMY

A. Setup.

1. Unless extenuating circumstances exist, patients should receive general anesthesia.
2. It is important to inspect the surgical technicians table for the necessary equipment and test the tracheostomy cuff prior to beginning the procedure.
3. Anesthesia provider should release the ET tube holder and ensure all tape is ready for removal upon the surgeon's request.

B. Positioning.

1. Do not overextend the neck and displace the second and third tracheal rings too far superiorly.
2. Maintain neutral positioning for patients with cervical spine injuries.

C. Procedure.

1. Perform a time-out.
2. Prepare neck with 2% chlorhexidine gluconate in 70% isopropyl alcohol combination solution (or equivalent). Ten percent povidone–iodine should only be used if the patient has an allergy or sensitivity to chlorhexidine.
3. Infiltrate the area of the incision with 1% lidocaine with epinephrine.
4. The incision should be made below the cricoid ring and above the third tracheal ring.
   a. Longitudinal has the advantage of avoiding the anterior jugular veins and facilitating a speedy procedure.
   b. Transverse incisions are more cosmetic.
5. Use a combination of blunt dissection and electrocautery through the midline raphe down to the pretracheal fascia using care to avoid injury to the thyroid, which often obstructs visualization.
   a. The surgeon may divide the thyroid with the use of electrocautery or suture ligation.
   b. The thyroid may be elevated out of the field by inserting the cricoid hook into the membrane just below the cricoid cartilage.
6. Once the pretracheal fascia has been reached, the trachea, cricoid cartilage, and third tracheal rings are identified using care to maintain midline integrity.
7. A portion of the anterior surface of the third tracheal ring is then excised or incised. This may be done in a variety of ways either by making a series of incisions in the shape of an H or by elevating a U-shaped flap of cartilage, or simply removing a small segment of the anterior ring. Prior to making the tracheal incision, the trachea may be stabilized and elevated with two stay sutures on either side of the midline using a permanent monofilament.
8. The trachea is then generously dilated with a tracheal dilator.
9. The surgeon next asks the anesthesiologist to retract the ET tube under direct visualization and inserts the tracheostomy into the wound carefully following the curve of the cannula and the tracheal anatomy to ensure proper positioning.

10. The obturator is removed, the inner cannula is inserted and attached to the ventilator circuit, and the balloon is inflated. Proper positioning is confirmed with end-tidal CO_2.
11. The tracheostomy is secured in 4 points with suture and tracheostomy ties.

D. Troubleshooting.

1. Ensure that a 6.5-mm internal diameter ET tube is available for use in an emergency situation if the tracheostomy inner cannula is not immediately available.
2. If stay sutures are placed, they should be secured to the patient's skin and remain in place until the first tracheostomy change to aid in tracheal identification should the tracheostomy become unintentionally dislodged soon after insertion.

VI. PERCUTANEOUS TRACHEOSTOMY

A. Setup and positioning.

1. Patient should be positioned as for an open procedure.
2. Kit and tracheostomy should be inspected for completeness and functionality.
3. Although series of blind percutaneous tracheostomy have been published, it is the opinion of these authors that performing this procedure under bronchoscopic guidance is preferred as it creates the safest, most easily reproducible conditions.
4. Perform a preprocedural endoscopic exam of the tracheobronchial tree for any obvious abnormalities.

B. Procedure (see Video 11-1).

1. Perform a time-out.
2. Prepare neck with 2% chlorhexidine gluconate in 70% isopropyl alcohol combination solution (or equivalent).
3. With the bronchoscope in place, slowly retract the ET tube until the first or second tracheal ring is able to be transilluminated exercising care not to extubate the patient.
4. Anesthetize the overlying skin with 1% lidocaine with epinephrine and make a longitudinal skin incision in the same location as for an open procedure.
5. Retract the bronchoscope into the lumen of the ET tube to protect it from damage.
6. Using a blunt instrument, gently apply pressure to the trachea in the midline over the second or third tracheal ring; confirm proper positioning under direct visualization with the bronchoscope.
7. Once an appropriate location in the midline of the anterior trachea has been chosen, the lumen of the trachea is accessed using a percutaneous needle. This is done perpendicular to the trachea itself and under direct visualization to avoid through and through tracheal perforation and associated esophageal injury.

8. Using Seldinger technique, a guidewire is threaded through the needle and into the trachea using care to ensure the guidewire passes distal down toward the carina. The needle is then removed.
9. The trachea is serially dilated (kits vary) until the tracheostomy can be easily passed over the wire.
10. The dilator/introducer and wire are removed; the inner cannula is inserted and connected to the ventilator circuit. Correct positioning is confirmed by end-tidal CO_2 as above, and the ET tube is subsequently removed.
11. The tracheostomy is secured in 4 points with sutures as well as with tracheostomy ties.

VII. SEMIOPEN TRACHEOSTOMY

A. This technique is a hybrid/variation of the open and percutaneous tracheostomies.
B. The use of ultrasonography may be advantageous.
C. This technique has a higher risk of tracheoesophageal fistula formation.

VIII. POSTPROCEDURE CONSIDERATIONS AND COMPLICATIONS

A. Chest x-ray (CXR).
   1. Studies have failed to demonstrate the routine postprocedural CXR to be cost-effective; however, it is often the standard of care in many institutions.
   2. Evaluate for proper tracheostomy positioning, bronchial plugging, and/or pneumothorax.

B. Tracheal stenosis.
   1. In the past, ET tubes had high-pressure/low-volume cuffs, which were associated with a higher incidence of tracheal stenosis in those who were intubated for prolonged periods. Newer ET tubes have high-volume/low-pressure cuffs.
   2. Traditionally, stenosis was felt to be more common with the open procedure; however, newer literature regarding this issue is controversial.
      a. Follow-up and practitioner experience appear to outweigh approach when determining risk for stenosis.
      b. While stenosis rates seem to be the same for open versus percutaneous tracheostomy, this problem occurs higher on the trachea and earlier in patients who undergo percutaneous tracheostomy when compared to those with tracheal stenosis after open tracheostomy.

C. Tracheoinnominate artery fistula is a rare and often rapidly fatal complication even if recognized early.
   1. Typically occurs in slender female patients with long gracile necks.
   2. Often this is due to selection of a site distal to the third tracheal ring for tracheostomy insertion and can be avoided by using care not to overextend the neck.

3. In patients who underwent percutaneous tracheostomy insertion, this complication may also arise in the setting of the needle being inserted into the trachea through the innominate artery.

D. Anterior tracheal injury and posterior perforation are more common in percutaneous tracheostomy and may result in pneumothorax and subcutaneous emphysema.

E. Dislodgement of tracheostomy.

1. Unintentional decannulation can occur at any time, in any tracheostomy regardless of the operative method for creation, and is potentially life-threatening.
2. Factors such as obesity, excessive secretions, granulation tissue, a patient with a short neck, and abnormal anatomy can all further complicate the picture.
3. A replacement tracheostomy tube set (inner and outer cannulae and the obturator) as well as one that is one size smaller should be kept by the patient's bedside as should appropriately sized suction catheters, an Ambu bag, and an ET tube that is half a size smaller than the outer diameter of the tracheostomy tube for rapid response in the setting of accidental decannulation.
4. Displacement is particularly difficult to manage early (i.e., within 7 days) after tracheostomy creation prior to maturation of the tract. During this period, the biggest risk of attempts to blindly reinsert a dislodged tracheostomy tube in an emergency situation is the formation of a blind passage. For this reason, orotracheal intubation is the safest option if any resistance to reinsertion of the tracheostomy tube (with obturator in place) is met.
5. The stay sutures placed during the open technique may be used to help identify the proper anatomy, keep the airway open, and facilitate reinsertion; however, evidentiary data supporting this technique are lacking.

IX. PERCUTANEOUS VERSUS OPEN TRACHEOSTOMY

A. Cost-efficacy studies have demonstrated the percutaneous tracheostomy to be superior to the open procedure with respect to periprocedural cost if the following conditions are met.

1. The procedure is performed in the patient's room in the ICU.
2. A single kit is used.
3. There are no procedural complications.

B. The percutaneous tracheostomy is also felt to be of superior efficiency as it does not require OR utilization and its total procedure time and cost are less.

C. Complication rates do not clearly favor one procedure over another in the currently published studies although it does appear that the above-described, dilational percutaneous technique may be associated with fewer instances of wound infection, bleeding, and death.

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The authors found no difference in moderate or severe complications between the two methods of tracheostomy.

11 Diagnostic Peritoneal Lavage and Paracentesis

Mark L. Shapiro and Vanessa Schroder

I. GENERAL PRINCIPLES OF DPL

A. Diagnostic peritoneal lavage (DPL) was first described in 1964 by Root as a method to identify the presence of hemoperitoneum in a hemodynamically unstable trauma patient.

B. Advantages.

1. Easy, fast, and versatile.
2. Can be performed in the trauma bay even in a patient otherwise too unstable to travel to computed tomography (CT) scan.
3. Allows for expeditious triaging of critically ill polytrauma patients.
4. DPL is sufficiently sensitive to detect small amounts of blood from minor injuries in stable patients with high-risk mechanisms of injury.

C. Definition of a positive DPL.

1. Blunt trauma.
   a. 10 mL blood on initial aspiration.
   b. RBC >100000/mm^3 in lavage fluid.
   c. WBC >500/mm^3.
   d. Amylase >175 units/dL.
   e. The presence of food, particulate matter, stool, or bile.
2. The criteria for a positive DPL in penetrating trauma are the same as for blunt trauma save for the red blood cell (RBC) count being lowered to 10000/mm^3 (or even lower at some institutions or in the setting of thoracoabdominal wounds).
3. In the case of a stable patient with an equivocal DPL, the catheter may be left in place and the lavage repeated in 2 to 3 hours.

II. ACCURACY

A. The accuracy of the physical exam for detecting intra-abdominal injuries is 55% to 65% in blunt trauma.

B. When done properly DPL is able to detect as little as 20 mL of blood.

1. The aspiration of 10 mL of frank blood in blunt and penetrating trauma patients has a positive predictive value of >90% for intra-abdominal injury.
2. The specificity of DPL for blood is very high, >95%; however, as DPL is unable to define the extent of intra-abdominal injuries, its sensitivity

for an injury requiring intervention is likely somewhat lower than this (especially in the case of blunt trauma).

3. This procedure is not sensitive for injuries to retroperitoneal structures, and conversely retroperitoneal injuries can lead to a false-positive DPL.

C. The accepted nontherapeutic laparotomy rate is 10% to 15% when the decision for laparotomy is based on the clinical situation and DPL alone.

III. INDICATIONS

A. Hypotension and the unstable trauma patient are the most common indications for DPL, and DPL will help delineate the etiology especially in a patient unable to give an adequate history of the traumatic event or participate in the physical exam.

1. Patients with blunt abdominal trauma have intra-abdominal injuries 13% of the time.
2. Hemorrhagic shock in blunt trauma is almost always due to intra-abdominal injury of a vascular structure or solid organ. Even if another extra-abdominal source of hemorrhage is present, the abdomen should be evaluated for an additional site of bleeding.
3. As many as 10% of patients with presumed isolated traumatic head injuries will also have intra-abdominal injuries.

B. In addition to the hypotensive, unstable patient, a DPL is may be indicated in several additional clinical scenarios.

1. Patients with abdominal pain or tenderness on exam, abdominal wall bruising (including a seat belt sign), or distention.
2. Patients with unreliable physical exams, equivocal imaging, and mechanisms of injury that place them at high risk for hollow viscus injury.
3. Polytrauma patients already undergoing general anesthesia.
4. Patients with penetrating injuries where there is concern for the involvement of multiple body compartments (i.e., transdiaphragmatic).
5. Locations where appropriate cross-sectional imaging is not rapidly available.

C. The final decision to perform the DPL rests with the trauma surgeon who will be operating on and caring for the patient long term and is based on his or her clinical judgment.

IV. CONTRAINDICATIONS

A. DPL is only absolutely contraindicated when the decision to proceed with laparotomy has already been made based on the patient's obvious traumatic injuries (i.e., penetrating abdominal wounds with evisceration).

B. Relative contraindications.

1. Patients with a history of multiple abdominal operations.
2. Patients with a distended abdomen including women in their second or third trimesters of pregnancy who have a higher risk of morbidity and mortality to both the mother and the baby.
3. Patients with obvious abdominal wall hematomas due to the high false-positive rate.
4. Lack of surgeon able to perform surgery.

V. OTHER DIAGNOSTIC MODALITIES (Fig. 11-1)

A. CT scan is a rapid and noninvasive method of evaluating for intra-abdominal injury that is reserved for hemodynamically stable traumatized patients.

1. CT has the benefits of identifying solid organ injuries that are likely amenable to nonoperative management (either close observation or interventional radiology) as well as being able to evaluate the retroperitoneum.
2. The downsides of CT scanning are cost, the need for IV contrast administration, as well as the inability to be used in unstable patients.

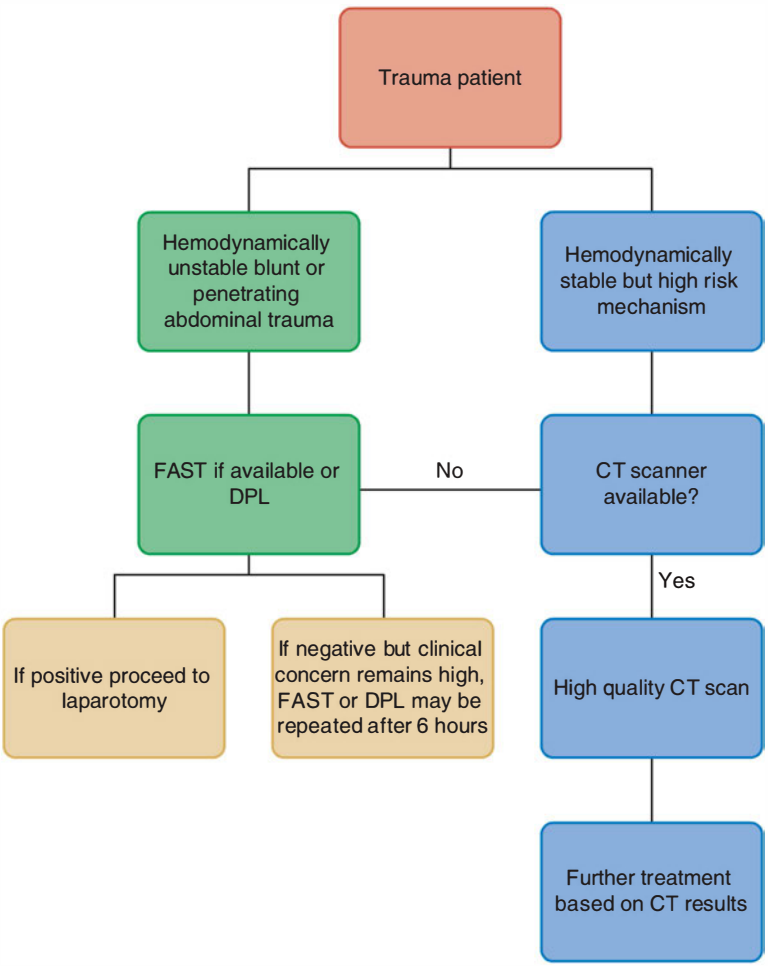

Figure 11-1. Proposed algorithm for evaluation of the abdomen in the trauma patient.

B. Focused assessment with sonography in trauma (FAST).

1. Ultrasound examination of Morrison pouch (right flank/hepatorenal space), the pouch of Douglas (pelvic), and the left flank/splenorenal recess in the abdomen for free fluid as well as the pericardium.
2. Performed during the secondary survey.
3. Advantages of FAST are speed, noninvasive nature of the test, the ability to be performed in the trauma bay in an unstable patient, and the ability for repeated, serial examinations.
4. Limitations of FAST are the inability to detect the source (solid organ injury vs. hollow viscus) or the character (blood vs. ascites vs. urine vs. succus) of the free fluid, lack of visualization of the retroperitoneum, and the need for larger volumes of fluid (>200 mL) for detection when compared to DPL.
5. 63% to 100% sensitivity.
6. 93% to 97% specificity.

C. Local wound exploration.

D. Laparotomy or laparoscopy (especially in penetrating trauma as a less invasive initial method to evaluate for violation of the peritoneal cavity).

VI. PROCEDURE

A. DPL is almost always done in the setting of trauma at the conclusion of the primary and secondary surveys. Control of the often chaotic situation and environment is essential as well as is the maintenance of universal and maximum barrier precautions.

B. Decompress hollow viscus.

1. The stomach is often distended from aggressive bag–valve–mask ventilation, anxiety-related aerophagia, or esophageal intubation and should be decompressed with an oro- or nasogastric tube.
2. Foley catheter.

C. Choice of incision location.

1. Above the umbilicus.
   a. In patients with pelvic fractures, the incision should be made above the arcuate line.
   b. In pregnant females, there is a risk of uterine perforation and DPL should be used with care as above.
2. Below the umbilicus is the choice in most patients as it facilitates placement of the catheter in the appropriate anatomic space.

D. Anesthetize the skin with 1% lidocaine with epinephrine (to reduce skin bleeding, which may obstruct the view or confound the results) over the length of the 2-cm incision.

E. Semiopen technique (most common).

1. Make a 2-cm incision through the skin to expose the fascia.
2. The fascia is grasped and elevated with two penetrating towel clamps.

3. The elevated fascia is incised in the midline.
4. A peritoneal dialysis catheter is inserted into the abdomen at a 45- to 60-degree angle aiming toward the pelvis and feeling for two distinct "pops" followed by a loss of resistance as the catheter enters the peritoneal cavity.
5. First an attempt is made at aspiration of free intraperitoneal blood. If 10 mL of blood is aspirated, the exam is considered positive and terminated.
6. If the diagnostic peritoneal aspirate is negative, the examiner proceeds with the DPL. One liter of crystalloid (or 25 mL/kg) is infused via two-way IV tubing, and then the bag is placed on the floor to drain dependently.
7. Interpretation should be deferred until at least 200 to 300 mL has been collected. At that time, 70 mL should be removed and sent to the lab for analysis and cell count.
8. The catheter may now be removed and the incision closed or left in place for a repeat lavage if the results are equivocal.

F. Complications.

1. Infection.
2. Iatrogenic intraperitoneal injury.
3. False positives due to imperfect technique leading to nontherapeutic laparotomies.

VII. GENERAL PRINCIPLES OF PARACENTESIS

A. A simple procedure performed at the patient's bedside by any properly trained practitioner involving the insertion of a needle into the peritoneal cavity and the aspiration of ascitic fluid for diagnostic or therapeutic purposes.

B. Prior to considering this intervention, the presence of a sufficient volume of ascites must be confirmed by a physical exam and/or imaging.

VIII. INDICATIONS

A. Diagnostic (10% of procedures performed) (Table 11-1).

1. If a paracentesis is done for diagnostic testing, only a small volume need be removed.
2. Fluid may be sent for examination and quantification as transudative (cirrhosis due to various etiologies, congestive heart failure, and nephrotic syndrome) or exudative (peritonitis, carcinomatosis, ischemic or obstructed bowel, or pancreaticobiliary inflammation) as well as to evaluate for infection.
3. Tests such as Gram stain, acid-fast bacilli smear, and culture and sensitivity; cytology; cell count, LDH, total protein, glucose, amylase, albumin, and triglyceride; and specific gravity may be ordered depending on the clinical situation.

TABLE 11-1 Common Laboratory Studies with Findings in the Diagnostic Paracentesis

	Gram stain	S/A (g/dL)	Glucose (mg/dL)	Specific gravity	Cytology	Total protein
Spontaneous bacterial peritonitis	+/–	1.1	<50	>1.016 if purulent	–	<1.0
Cirrhosis	–	>1.1	–	<1.016	–	<2.5
Congestive heart failure	–	>1.1	–	Variable <1.016	–	>2.5
Neoplastic process	–	<1.1 (but >1.1 with hepatic metastases)	Normal to low	Variable >1.016	+	>2.5 (can be <3 if liver replaced by tumor)
Nephrosis	–	<1.1	–	<1.016	–	<2.5

S/A, serum albumin/ascites albumin gradient.

B. Therapeutic (90% of procedures performed).

1. Large-volume therapeutic paracentesis is defined as the removal of at least 5 L of ascites.
2. Large-volume fluid removal can improve symptoms of discomfort from distention as well as improve pulmonary compromise.
3. When ascites is removed for these purposes (especially in a repeated fashion when patients may lose large amounts of protein), one may choose to administer albumin although its use remains controversial.

IX. CONTRAINDICATIONS

A. There are no absolute contraindications.

1. Potential complications related to each relative contraindication can often be easily avoided with careful preprocedure assessment and planning.
2. In the case of diagnostic paracentesis, the benefits of prompt fluid evaluation to tailor treatment almost always outweigh the risks.

B. Disseminated intravascular coagulation (although coagulopathy in and of itself is not a contraindication and several trials have documented <0.5% bleeding complications in patients with elevated international normalized ratios (INRs) or thrombocytopenia).

C. Pregnancy.

D. Ileus with small bowel or colonic distention.

E. Organomegaly.

F. Multiple prior abdominal operations.

X. PROCEDURE

- **A.** Do not delay. Especially in the setting of diagnostic paracentesis, delays may translate to serious complications for the patient.
- **B.** It is not necessary to correct the INR.
- **C.** Maintain universal precautions and sterile technique; obtain informed consent; and perform a time-out.
- **D.** As discussed above, image guidance may be used, most commonly ultrasound.
- **E.** Site selection.
  1. Position the patient supine in almost every case (rolled slightly to the left if using the left lower quadrant (LLQ) as your site).
  2. In the midline about 3 cm from the umbilicus had been a common choice due to the lack of vascularity in the midline. A location inferior to the umbilicus will avoid a potentially recanalized umbilical vein especially in patients with portal hypertension.
  3. In recent years a move has been made to choosing a site lateral to the rectus in the left or right lower quadrant to accommodate a more obese population. The abdomen has been shown to be thinner in the LLQ with a deeper fluid pocket.
  4. If ultrasound is not available, a suitable site may be identified by measuring two fingerbreadths medial to and cephalad to the anterior superior iliac spine.
  5. Avoid any surgical scars by several centimeters and the inferior epigastric artery (which is contained within the rectus sheath).
- **F.** Anesthetize the overlying skin with 1% lidocaine with epinephrine to make a skin wheal.
- **G.** Retract the skin laterally or downward to utilize the Z-track technique (as for intramuscular injections). This decreases the risk of a postprocedure ascites leak.
- **H.** Insert the paracentesis catheter using Seldinger technique into the peritoneal cavity aspirating intermittently with a syringe until there is return of ascitic fluid.
- **I.** Once the peritoneal cavity has been entered, the needle is stabilized, and the syringe disconnected, ascitic fluid should drip from the hub of the needle.
- **J.** If paracentesis is being performed for diagnostic purposes, the aspiration of 50 mL should be sufficient.
- **K.** If paracentesis is being performed for therapeutic purposes, the catheter is then connected via IV tubing to a negative-pressure vacuum bottle.
- **L.** If a designated paracentesis kit/catheter is not available, the procedure may be performed with an angiocatheter, spinal needle, or 18- to 22-gauge needle.
- **M.** Remove the needle or catheter and apply a sterile dressing the site.

XI. COMPLICATIONS

- **A.** The most common complication is ascites leak (5%).
- **B.** Bleeding is very rare (see above section on DIC).
- **C.** Perforation of hollow viscus (occurs in approximately 6/1,000 paracenteses).
- **D.** Infection generally only occurs in the setting of perforation of a hollow viscus.
- **E.** Exacerbation of the underlying disease process or its symptoms such as encephalopathy, renal failure, electrolyte imbalances, and hypotension.

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12 Gastroesophageal Balloon Tamponade for Acute Variceal Hemorrhage

Marie T. Pavini

I. GENERAL PRINCIPLES

A. Definitions.

1. Esophageal variceal hemorrhage: an acute, severe, dramatic complication of the patient with portal hypertension that carries a high mortality and significant incidence of recurrence.

2. Gastroesophageal balloon tamponade: a multilumenal tube with esophageal and gastric inflatable cuffs that can be inflated to compress esophageal varices and gastric cardia submucosal veins.

II. ALTERNATIVE PROCEDURES AND THERAPEUTICS (Fig. 12-1)

A. Band ligation is a first-line therapy offering a lower incidence and severity of complications and greater success for controlling bleeding.

B. Sclerotherapy is also a first-line therapy carrying a more desirable complication and success profile than does balloon tamponade.

C. Combined vasoactive pharmacologic therapy and balloon tamponade can control hemorrhage in 90% of cases.

D. Octreotide or combination vasopressin and nitroglycerin diminishes portal vein pressure, while emergency endoscopy is performed to confirm the diagnosis.

E. Percutaneous transhepatic embolization is recommended in poor-risk patients who do not stop bleeding despite other measures.

F. Esophageal devascularization with gastroesophageal stapling can be performed for patients without cirrhosis as well as for low-risk patients with cirrhosis.

G. Transjugular intrahepatic portosystemic shunt (TIPS) can be used as a bridge to transplant.

H. Esophageal transection is an extreme measure used to control bleeding.

I. Distal splenorenal shunt is performed to decrease portal hypertension.

J. Removable self-expanding metal esophageal stents placed without radiographic assistance are being studied.

III. INDICATIONS

A. Therapeutic.

1. Gastroesophageal balloon tamponade is indicated in patients with esophageal variceal hemorrhage in whom neither sclerotherapy nor band ligation

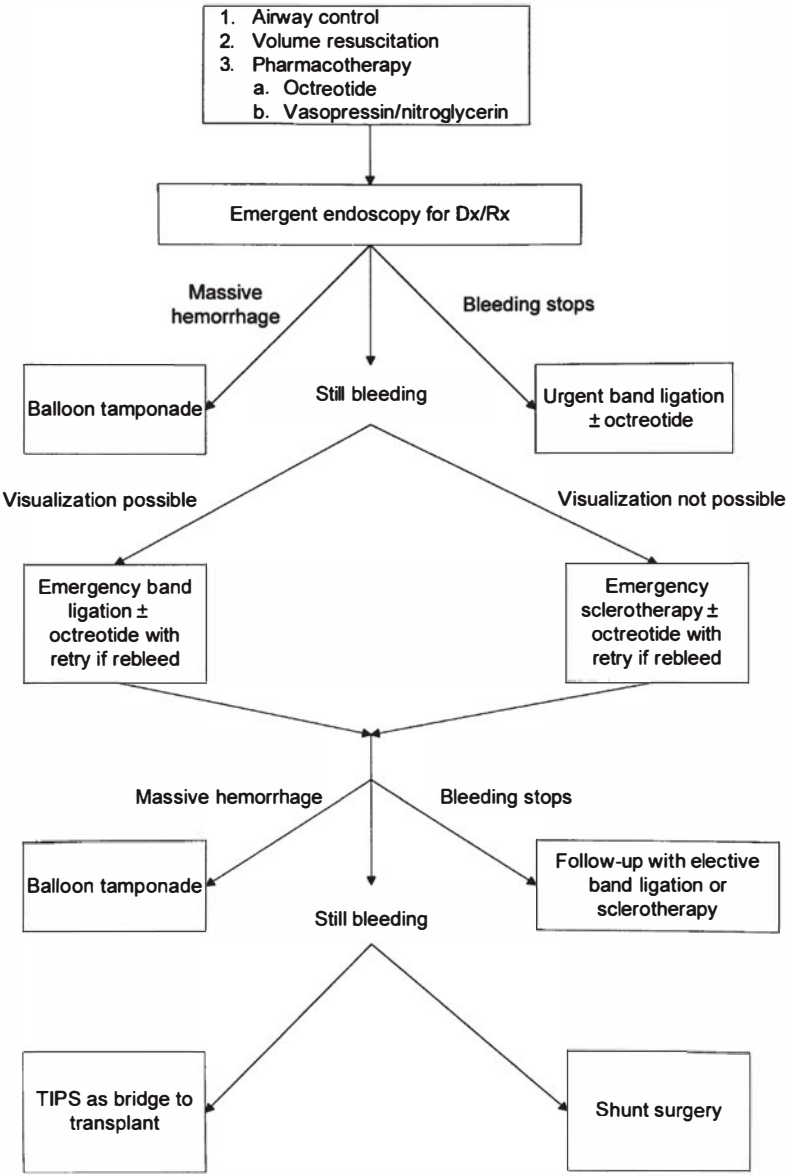

Figure 12-1. Management of esophageal variceal hemorrhage. Dx, diagnosis; Rx, therapy; TIPS, transjugular intrahepatic portosystemic shunt. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012, with permission.)

is technically possible or readily available or in whom sclerotherapy or band ligation has failed.

B. Diagnostic.

1. With use of the infragastric balloon suction port, it is possible to differentiate esophageal from gastric variceal bleeding.

IV. CONTRAINDICATIONS

A. Balloon tamponade is contraindicated in patients with recent esophageal surgery or esophageal stricture.

B. Some authors do not recommend balloon tamponade when a hiatal hernia is present, although there are reports of successful hemorrhage control in such patients.

V. PROCEDURE

A. Preprocedure considerations.

1. Hemodynamics and resuscitation.

a. Endotracheal intubation should be performed for the majority of patients who will undergo balloon tamponade for airway protection from blood and oropharyngeal secretions. It also allows for the safe administration of sedatives and analgesics.

b. Adequate intravenous access should be obtained with large-bore venous catheters and fluid resuscitation undertaken with crystalloid and colloid fluids.

c. A central venous catheter, bedside ultrasound, pulmonary artery catheter, or other hemodynamic monitor may be required to ensure that intravascular filling pressures are adequate without increasing portal pressure to such an extent as to exacerbate variceal bleeding.

d. Four to six units of packed red cells should always be available in case of severe recurrent bleeding that commonly occurs in these patients.

e. Coagulopathy should be treated acutely with fresh frozen plasma and platelets.

f. Octreotide or combination vasopressin and nitroglycerin should be administered and as part of initial resuscitation.

g. Antibiotic therapy should be initiated.

2. Initial procedural intervention in the nonhemorrhaging patient.

a. Placement of an Ewald tube and aggressive lavage and suctioning of the stomach and duodenum facilitate endoscopy, diminish the risk of aspiration, and may help control hemorrhage from causes other than esophageal varices.

b. The diagnostic endoscopic procedure should be done as soon as the patient is stabilized after basic resuscitation. Endoscopy is performed in the intensive care unit or operating room under controlled monitoring and with adequate equipment and personnel. An endoscope with a large suction channel should be used.

B. Equipment.

1. Although several studies have published combined experience with tubes such as the Linton and Nachlas tube, the techniques described here are limited to the use of the Minnesota (Fig. 12-2) and Sengstaken-Blakemore (Fig. 12-3) tubes. The Minnesota tube has a fourth lumen for hypopharyngeal suctioning. When using a Sengstaken-Blakemore tube, an 18 Fr nasogastric or orogastric tube should be positioned above the esophageal balloon as described below.
2. A helmet with a facemask such as a hockey or American football helmet may be placed on the patient's head to properly align the tube for traction if required. A bed with an overhead frame may be used as well. Weights can be applied as needed.
3. Pressure gauges for the balloons as well as clamps and scissors for the tubing will be necessary for proper usage.

C. Technique.

1. All lumens should be patent, and the balloons should be inflated and checked for leaks. If using the Sengstaken-Blakemore tube, an 18 Fr nasogastric or orogastric tube should be secured above the esophageal balloon with surgical ties. The tube should be generously lubricated with lidocaine jelly. A time-out should be performed.
2. The tube can be inserted through the nose or mouth; however, the nasal route is not recommended in patients with coagulopathy. The tube is passed into the stomach (Fig. 12-4).
3. The position of the gastric tube must be confirmed radiologically at this time.

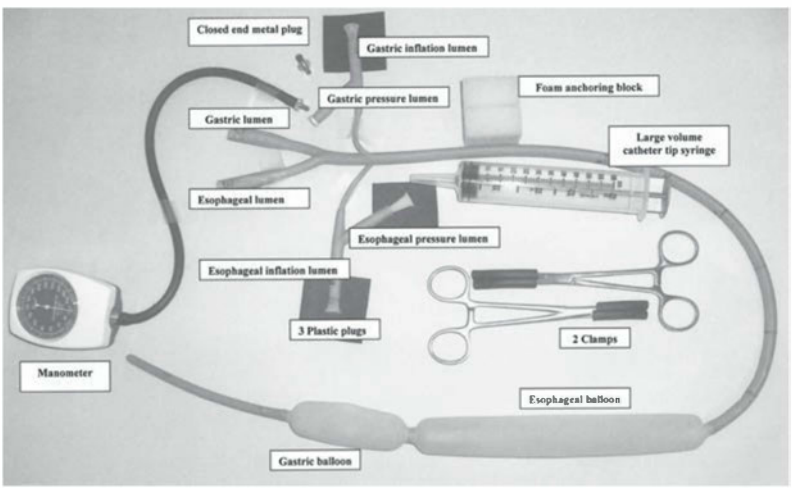

Figure 12-2. Minnesota tube. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012, with permission.)

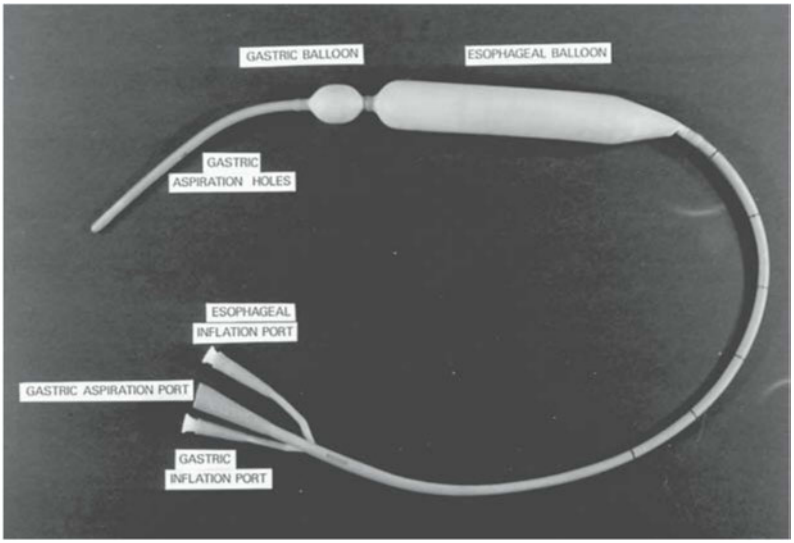

Figure 12-3. Sengstaken-Blakemore tube. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012, with permission.)

4. The gastric balloon is inflated with no more than 80 mL of air, and a portable radiograph is obtained that includes the upper abdomen and lower chest. Ultrasonography is an alternative method of verification of tube placement.
5. When it is confirmed that the gastric balloon is below the diaphragm, it should be further inflated slowly to a volume of 250 to 300 mL. The gastric balloon of the Minnesota tube can be inflated to 450 mL. Tube inlets should be clamped with rubber-shod hemostats after insufflation.
6. Hemorrhage is frequently controlled with insufflation of the gastric balloon alone without applying traction; but, in patients with torrential hemorrhage, it is necessary to apply traction (*vide infra*). If the bleeding continues, the esophageal balloon should be inflated to a pressure of approximately 45 mm Hg (bedside manometer). This pressure should be monitored and maintained. Some authors advocate inflation of the esophageal balloon immediately after insertion (see Section VI.C).
7. When the nasal route is used, traction should not be applied against the nostril because this can easily cause skin and cartilage necrosis. When traction is required, the tube should be attached to a cord that is passed over a pulley in a bed with an overhead orthopedic frame and aligned directly as it comes out of the nose to avoid contact with the nostril. This system allows maintenance of traction with a known weight (500 to 1,500 g) that is easily measured and constant.

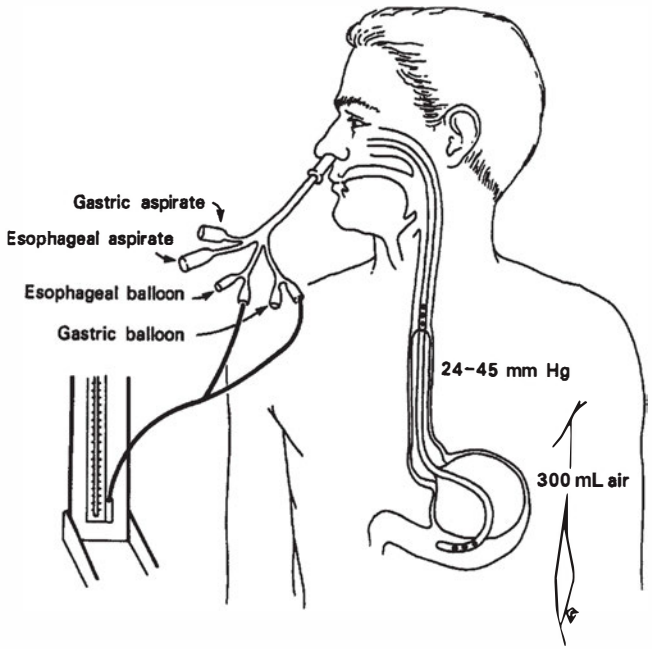

Figure 12-4. Proper positioning of the Minnesota tube. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012, with permission.)

8. When the tube is inserted through the mouth, traction is better applied by placing a helmet with attached facemask on the patient and attaching the tube to the face mask of the helmet after a known weight (500 to 1,500 g) is applied for tension. Pressure sores can occur in the head and forehead if the helmet does not fit properly or it is used for a prolonged period of time. Several authors recommend overhead traction for oral insertions as well as for nasal insertions.
9. The gastric lumen is placed on intermittent suction. The Minnesota tube has an esophageal lumen that can also be placed on low intermittent suction. If the Sengstaken-Blakemore tube is used, then the nasogastric or orogastric tube that is positioned above the esophageal balloon (see Section V.B.1) should be set to continuous suction.

VI. POSTPROCEDURE CONSIDERATIONS

A. Monitoring.

1. The tautness and inflation of the balloons should be checked an hour after insertion and periodically by experienced personnel.
2. The position of the tube should be monitored radiographically or by ultrasound every 24 hours (Fig. 12-5) or sooner if there is suspicion of

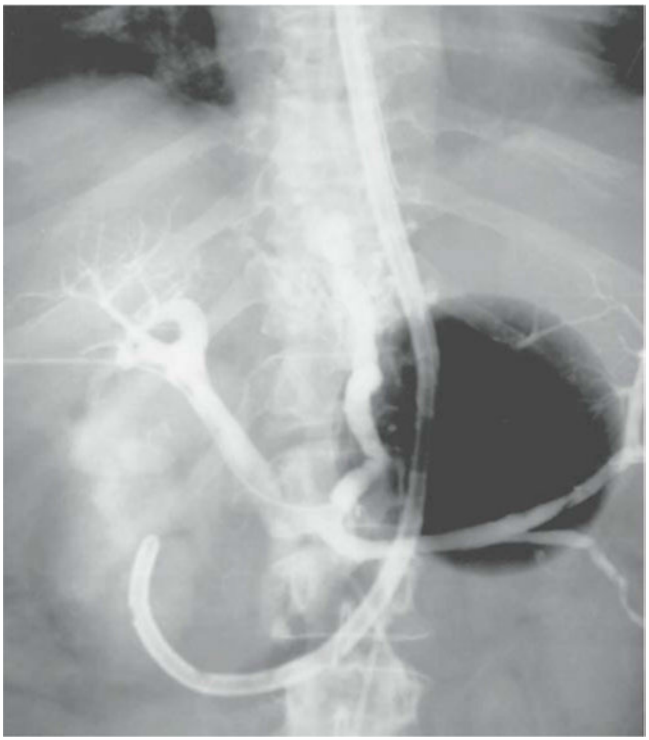

Figure 12-5. Radiograph showing correct position of the tube; the gastric balloon is below the diaphragm. (Courtesy of Ashley Davidoff, MD.) (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012, with permission.)

tube displacement. A pair of scissors should be at the bedside in case the balloon port needs to be cut for rapid decompression because the balloon can migrate and acutely obstruct the airway.

B. Weaning and removal.

1. The tube should be left in place for approximately 24 hours. The gastric balloon tamponade can be maintained continuously up to 48 hours. The esophageal balloon, however, must be deflated for 30 minutes every 8 hours.
2. Once hemorrhage is controlled, the esophageal balloon is deflated first; the gastric balloon is left inflated for an additional 24 to 48 hours. If there is no evidence of bleeding, the gastric balloon is deflated, and the tube is left in place 24 hours longer. If bleeding recurs, the appropriate balloon is reinflated. The tube is removed if no further bleeding occurs.

C. Complications.

1. The incidence of complications that are a direct cause of death in published reports ranges from 0% to 20%.
2. Tube migration (inadequate gastric balloon inflation or excessive traction).
   a. Acute laryngeal obstruction.
   b. Tracheal rupture.
3. Perforation of the esophagus.
4. Aspiration pneumonia.
5. Mucosal ulceration of the gastroesophageal junction is related to prolonged traction time (>36 hours).
6. Impaction: inability to deflate the balloon. Occasionally, surgery is required to remove the balloon.
7. Necrosis of the nostrils.
8. Nasopharyngeal bleeding.
9. Compression of the left atrium by the gastric balloon with subsequent cardiogenic shock.

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13 Placement of Feeding Tubes

Ulises Torres and Rupal Patel

I. GENERAL PRINCIPLES

A. Introduction.

1. Enteral nutrition (EN) in the critically ill patient compared to parenteral nutrition.

a. Maintains the integrity of the intestinal mucosal barrier.

b. Decreases infectious morbidity and improves wound healing.

c. Reduces cost.

d. EN should be instituted if possible in the first few days after admission to the critical care unit unless the patient exhibits signs of intestinal ischemia or is hemodynamically compromised.

B. Classification.

1. Administration of EN can be classified according to anatomic location of the feeding tube. The selection of the device requires an evaluation of the patient's disease state, gastrointestinal (GI) anatomy, past surgical history, gastric and jejunal motility, and the estimated time of therapy.

a. Short-term administration (<4 weeks).

i. Can be administered through nasogastric (NG) or orogastric (OG) (polyvinyl chloride tube, 16 or 18 Fr), nasoduodenal, or nasojejunal fine-bore tubes (silicone or polyurethane feeding tube, 6 to 14 Fr).

ii. Multilumen tubes allow gastric decompression while delivering feeding formula into the jejunum. These are not required in the ICU unless gastric feeding intolerance is present.

b. Long-term administration (>4 weeks).

i. Access routes for long-term EN include esophagostomy, gastrostomy, duodenostomy, gastrojejunostomy (Moss tube), and jejunostomy. These tubes are for patients with persistent dysphagia (Fig. 13-1).

2. Anatomic location of the feeding tube.

a. Gastric feeding relies on a functional stomach free of delayed gastric emptying, obstruction, or fistula.

b. Feeding into the duodenum does not decrease regurgitation but has demonstrated better levels of nutrition than gastric feedings; infusion into the jejunum is associated with the lowest risk of aspiration and is indicated for patients with gastroparesis and pancreatitis and also for those patients who need gastric decompression while feeding distally in the bowel (gastrojejunostomy tube).

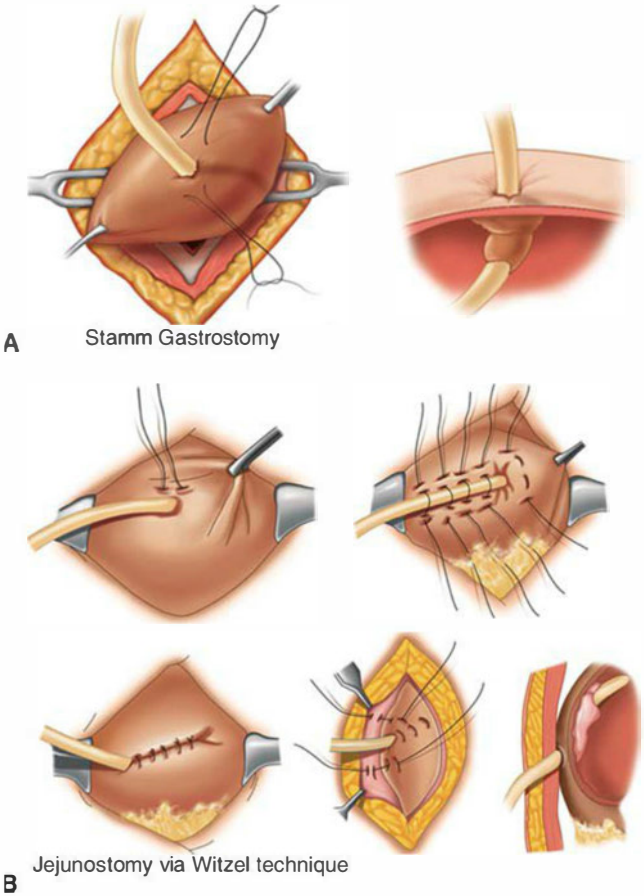

Figure 13-1. Long-term enteral devices. **A:** Steps for Stamm Gastrostomy. **B:** Steps for Jejunostomy.

C. Contraindications for surgical placement of tube (percutaneous endoscopic gastrotomy [PEG] and open technique).

1. Absolute contraindications include coagulopathy, strictures of pharynx or esophagus (contraindication for placement of gastroscope), and abdominal wall infections.
2. Relative contraindications include severe ascites, gastric cancer, gastric ulcer, and recent banding of bleeding esophageal or gastric varices and morbid obesity.

D. Contraindications for tube feeding.

1. Absolute contraindications include intestinal obstruction, severe upper GI hemorrhage, or severe mesenteric ischemia.
2. Relative contraindications include
   a. Gastric feeding in patients with increased risk of pulmonary aspiration.

b. Enterocutaneous fistulas, severe inflammatory bowel disease, severe malabsorption, and severe short-gut syndrome.

II. PROCEDURE

A. Placement of nasoenteral feeding tubes or short-term feeding tubes.

1. Appropriate length of the feeding tube: stomach, 30 to 36 in.; duodenum, 43 in.; and jejunum, at least 48 in. (Most tubes are radiopaque and have a tungsten-weighted tip or a stylet to facilitate passage into the duodenum.) Use of an electromagnetic system that allows real-time tracking of insertion of the feeding tube will minimize the risk of placement of the tube within the tracheobronchial tree (Fig. 13-2).
2. The universal protocol should be followed. With the patient in the right lateral decubitus position (if not contraindicated; supine if the electromagnetic systems is used), the tube is lubricated and advanced through the patient's nose into the stomach. Use of a carbon dioxide detector will also alert the clinician to tracheal misdirection of the tube. The submersion technique can be used to identify the location of the tube in the airway in addition to the other techniques but should not be used as the sole means to identify tracheal placement (Fig. 13-3).

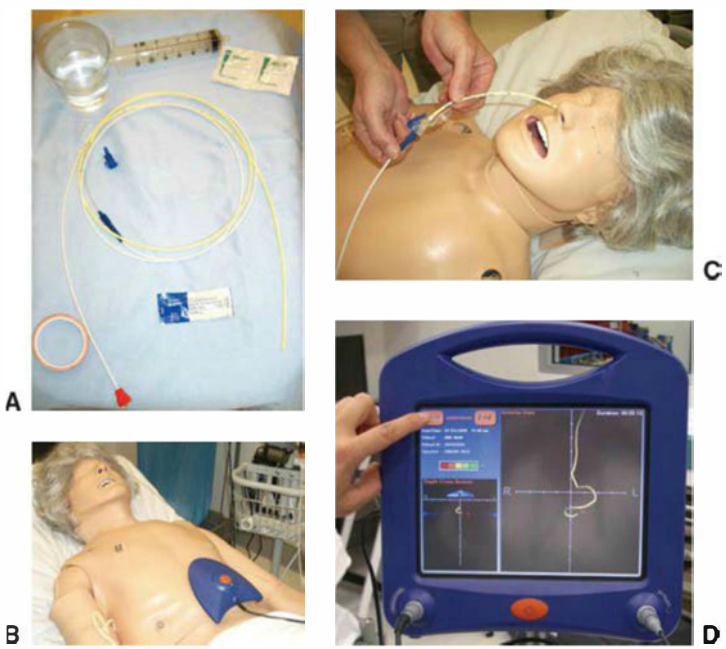

Figure 13-2. **A:** Equipment. **B:** Positioning. **C:** Tube placement. **D:** Confirmation by electromagnetic sensor.

Figure 13-3. Bubbles are seen through the air port after accidental insertion in the airway.

3. Confirmation of correct placement must be made by x-ray, with observation of the whole length of the tube.
4. A prokinetic agent such as erythromycin (500 mg IV) may facilitate passage of the tube into the small bowel; metoclopramide has been shown to be ineffective.
5. The tube is securely taped to the patient's forehead or cheek without tension.
6. If the tube is placed for duodenal or jejunal feeding, a loop of 6 to 8 in. long may be left extending from the nose, and the tube may be advanced 1 to 2 in. every hour.
7. If the tube does not migrate into the duodenum over several hours, endoscopic assistance or fluoroscopic guidance can be attempted.
   a. After sedation and topical anesthesia, a nasoenteric feeding tube (43 to 48 in.) with an inner wire stylet is passed transnasally into the stomach.
   b. The endoscope is then advanced into the gastric lumen, and endoscopy forceps are passed through the biopsy channel to grasp the tip of the enteral feeding tube.
   c. The endoscope, along with the enteral feeding tube, is advanced into the duodenum as far as possible; the endoscopy forceps and feeding tube remain in position as the endoscope is withdrawn back into the stomach.
   d. The forceps are opened and withdrawn carefully back into the stomach.
   e. The feeding tube is usually lodged in the second portion of the duodenum.
   f. The portion of the feeding tube that is redundant in the stomach is advanced slowly into the duodenum with the endoscopy forceps.

B. Placement of long-term feeding tube.

1. Indications: need for prolonged EN.

2. Consideration.

a. If patients have a thick abdominal wall (usually >4 cm), there is a higher risk of tube dislodgment, and an open procedure should be considered.

b. If the patients have ascites, a PEG should not be performed because a track will not form and the patient is at higher risk of developing complications.

3. Procedure: placement of PEG tube.

a. After a time-out, adequate sedation, and prophylactic antibiotics, the posterior pharynx is anesthetized.

b. A flexible gastroscope is inserted into the stomach that is insufflated with air.

c. Digital pressure to the patient's anterior abdominal wall in the left subcostal area (2 cm below costal margin) identifies the area of brightest transillumination.

i. The indentation in the stomach created by digital pressure must be identified endoscopically; otherwise, another site should be chosen.

d. After prepping with an alcoholic chlorhexidine solution and local anesthesia, a small skin incision is made.

e. A polypectomy snare is introduced through the endoscope biopsy channel.

f. An introducer catheter is passed into the stomach and through loop of snare, under direct endoscopic visual guidance.

g. After removal of the stylet, a looped guidewire is introduced through the catheter into the stomach.

h. The cannula is withdrawn slowly, so that the snare grasps the wire.

i. The gastroscope is removed from the stomach, and the end of the transgastric wire exiting the patient's mouth is tied to a gastrostomy tube.

j. The wire exiting from the abdominal wall is pulled, while the endoscopist guides the lubricated gastrostomy tube into the stomach and then out through the abdominal wall.

k. The gastroscope is reinserted into the stomach to confirm adequate placement and rule out bleeding. (The intraluminal portion of the tube should contact the mucosa, but excessive tension on the tube should be avoided.)

l. The phalange is attached to the PEG tube to secure it in place.

4. Procedure: open Stamm gastrostomy tube (G tube).

a. After general anesthesia and prophylactic antibiotics, the abdomen is prepped and draped in sterile fashion, and a time-out is performed.

b. An upper midline incision is made, and the linea alba is incised to gain access to peritoneal cavity.

c. The stomach is identified, and a location for the gastrostomy site is selected.

d. Two purse-string sutures are placed in a concentric fashion around the intended gastrotomy site.

e. A small incision is made in the left upper quadrant and is dissected down to the anterior abdominal wall.
f. The feeding tube is pulled through the anterior abdominal wall and into the field.
g. A gastrotomy in the center of the purse string is made using electrocautery, and the tube is advanced into the stomach.
h. The purse-string sutures are secured in place.
i. The stomach is then tacked to the anterior abdominal wall to prevent leakage or torsion.
j. The fascia is closed with a running suture, and the skin is closed with staples.
k. The catheter is then secured to the skin.

5. Procedure: percutaneous endoscopic jejunostomy (PEJ) tube.
a. The PEJ tube allows for simultaneous gastric decompression and duodenal or jejunal enteral feeding if a small feeding tube is attached and passed through the gastrostomy tube and advanced endoscopically into the duodenum or jejunum.
b. When the PEG is in position, a guidewire is passed through the PEG, grasped using endoscopy forceps, and passed into the duodenum as distally as possible.
c. The jejunal tube is then passed over the guidewire through the PEG into the distal duodenum and is advanced into the jejunum. The endoscope is then withdrawn (Fig. 13-1).

III. POSTPROCEDURE COMPLICATIONS TO BE AWARE OF

A. Hemorrhage (intra- and retroperitoneal, abdominal wall).
B. Tube dislodgement causing peritonitis.
C. Necrosis of gastric wall from an external phalange that is too snug.
D. Injury to other organs (such as small bowel, colon, spleen).
E. Leakage around the tube.

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14 Cerebrospinal Fluid Aspiration

Raimis Matulionis

I. GENERAL PRINCIPLES

A. The cerebrospinal fluid (CSF) profile includes glucose and protein values, a cell count, a Gram stain, cultures, and an opening pressure measurement.

1. CSF glucose.

a. Normally equivalent to two-thirds of a serum glucose measurement made 2 hours before the CSF measurement. Increased CSF glucose is a nonspecific finding and usually reflects hyperglycemia. Decreased levels are the result of any inflammatory, infectious, or neoplastic meningeal disorder.

2. CSF protein.

a. Content is usually <0.5% of that in plasma. Elevated level in the CSF is an indicator of central nervous system (CNS) pathology. Low levels are seen in patients with pseudotumor cerebri, acute water intoxication, and leukemia.

3. CSF cell count.

a. Normal count includes no erythrocytes and a maximum of five leukocytes per milliliter. Microscopic examination is helpful for identifying cells from CNS primary or metastatic tumors and differentiation from inflammatory disorders.

II. INDICATIONS

A. CSF analyses for diagnostic purposes: A computed tomography (CT) scan of the head should be strongly considered before performing a lumbar puncture (LP) in patients with dilated or poorly reactive pupils, papilledema, ocular palsies, hemiparesis, a recent history of focal seizures, a rapid or major decrease in the level of consciousness, bradycardia, irregular respirations, tonic seizures, or decerebrate or decorticate posturing.

1. *Hemorrhage.*

a. An LP is indicated if the CT scan of the head is not diagnostic or a clinical history and presentation is atypical. LP should not be performed without prior CT—supratentorial conditions with increased intracranial pressure (ICP) may result in transtentorial herniation.

2. *Infection.*

a. CSF evaluation is the most important aspect of the laboratory diagnosis of meningitis. It includes a Gram stain, cell count with

differential, protein and glucose levels, and aerobic and anaerobic cultures with antibiotic sensitivities.

b. If tuberculosis or fungal infection is suspected, the fluid is analyzed by acid-fast stain, India ink preparation, mycobacterial culture, cryptococcal antigen testing, and fungal culture.

c. Immunocompromised patients require more extensive cultures.

d. Testing for nonbacterial nonfungal pathogens includes viral culture, immunoglobulin titers, or polymerase chain reaction tests for herpes simplex, eastern equine encephalitis, West Nile, varicella-zoster, cytomegalovirus, Epstein-Barr virus, and *Toxoplasma*.

3. *Shunt system failure.*

a. Ventriculoperitoneal (VP) shunt, the most common system, consists of a ventricular catheter, reservoir, and valve complex at the skull and a catheter that continues subcutaneously into the peritoneum, jugular vein, pleura, or urinary bladder. Shunt failure is often due to obstruction, disconnection, or infection of the shunt system. If failure is suspected, a CT scan should be performed immediately. Aspiration from the reservoir or valve system performed to determine patency and to collect CSF for testing for an infectious process.

4. *Benign intracranial hypertension (pseudotumor cerebri).*

a. Occurs in young persons, often obese women. ICP elevation without focal deficits. Absence of ventriculomegaly and mass lesions. Symptoms develop over several months: headache (most common), dizziness, blurred vision, diplopia, transient visual obscurations, and abnormal facial sensations. Objective signs: visual impairment, papilledema, and sixth nerve palsy; LP demonstrates elevated ICP (up to 40 cm H_2O). Serial daily punctures can be therapeutic, with CSF aspirated until closing pressure is within normal limits (<20 cm H_2O).

5. *Neoplastic diseases of the CNS.*

a. The subarachnoid space can be infiltrated by various primary or secondary tumors. CSF cytology study can detect the presence of neoplastic cells; flow cytometric analysis can provide important information regarding clonality and the tissue source of CSF cells. CSF analysis for autoantibodies can be helpful for the diagnosis of some paraneoplastic syndromes.

6. *Other neurologic disorders.*

a. Multiple sclerosis: elevated immunoglobulin G and oligoclonal bands; antibodies against cardiolipin synthetic lecithin (CSL) is a sensitive and specific diagnostic test.

b. Alzheimer disease: elevated τ protein and decreased amyloid-β peptide.

c. Guillain-Barré syndrome: Antiganglioside (anti-GM1) antibodies are diagnostic, and cytoalbumin dissociation (elevated CSF protein without leukocytosis) is suggestive of this diagnosis.

B. CSF access for therapeutic intervention.

1. *Fistulas.*

a. The most common presentations following trauma: basilar skull fracture that traverses the ethmoid bone and frontal sinus causing CSF rhinorrhea or fracture that follows the long axis of petrous bone resulting in hemotympanum and CSF otorrhea (when the tympanic membrane is ruptured).

b. Delayed CSF leaks are common: Fistulae can be occluded with adhesions, hematoma, or herniated brain tissue. Diagnosis made during clinical examination. If clinical examination is uncertain, laboratory characterization is necessary.

i. Testing for glucose might be misleading as glucose is present in nasal secretions, and the use of elevated chloride levels is not accurate.

ii. Identification of β_2-transferrin—the most accurate diagnostic test for CSF. β_2-transferrin is produced by neuraminidase in the brain and is uniquely found in the spinal fluid and perilymph.

c. First-line treatment of a leak consists of postural drainage by keeping the patient's head elevated for several days. Nonoperative approaches including placement of a lumbar drainage catheter and daily LPs should be considered when conservative therapy fails.

C. *Intracranial hypertension.*

1. Can cause significant neurologic morbidity and mortality. Access to intracranial CSF space can be diagnostic or therapeutic. Most common ICP monitor used for access and to measure ICP is a ventriculostomy. It can be used to treat intracranial hypertension by allowing CSF drainage. Indications include head trauma, ischemic cerebral insults, obstructive hydrocephalus, aneurysmal subarachnoid hemorrhage (SAH), and spontaneous cerebral hematoma.

D. *Drug therapy.*

1. Can be a route of administration for chemotherapeutic agents and antibiotics. Intrathecal injections of various agents through LP or intraventricular injections through an implanted reservoir for treatment of lymphoma, leukemia, or fungal infection.

III. PROCEDURE

A. *LP* is a common procedure that rarely requires radiologic or other assistance.

1. Contraindications.

a. Skin infection at the entry site.

b. Anticoagulation.

c. Blood dyscrasias.

d. Known spinal subarachnoid block.

e. Known spinal cord arteriovenous malformations.

f. Papilledema in the presence of supratentorial masses.

g. Posterior fossa lesions.

2. Steps for LP.
   a. A time-out is performed and the universal protocol is followed.
   b. The patient is placed in the lateral knee–chest position or is sitting while leaning forward over a table.
   c. The area around L3-4 is prepped with an aqueous chlorhexidine solution or equivalent.
   d. A mask and sterile gloves are worn, and a fenestrated sterile drape is placed at the site.
   e. Local anesthetic is injected subcutaneously using a 25- or 27-gauge needle.
   f. A 1.5-in. needle is then inserted through the skin wheal, and additional local anesthetic is injected along the midline.
   g. The point of skin entry is midline between the spinous processes of L3-4, at the level of the superior iliac crests.
   h. The needle (usually 3.5 in., 18 or 20 gauge) is advanced with the stylet or obturator in place.
   i. The bevel of the needle should be parallel to the longitudinal fibers of the dura or to the spinal column and oriented rostrally at an angle of approximately 30 degrees to the skin and aiming toward the umbilicus.
   j. When properly oriented, the needle passes through the following structures: skin → superficial fascia → supraspinous ligament → interspinous ligament → ligamentum flavum → epidural space with its fatty areolar tissue and internal vertebral plexus → dura → arachnoid membrane.
   k. An 18- to 20-gauge spinal needle should be used for pressure measurement.
      i. The opening pressure is best measured with the patient's legs relaxed and extended partly from the knee–chest position. Once collected, the closing pressure is measured before needle withdrawal. Measurements are not accurate if performed while the patient is sitting because of the hydrostatic pressure of the CSF column.
   l. Hemorrhage is uncommon but is possible for patients with bleeding disorders or after the administration of anticoagulation.
   m. Spinal SAH can result in blockage of CSF outflow with subsequent back and radicular pain, sphincter disturbances, and even paraparesis.
   n. Spinal subdural hematoma is similarly infrequent, but it is associated with significant morbidity.
   o. Surgical intervention for clot evacuation must be accomplished promptly.
   p. Infection by introduction of skin flora into the subarachnoid space causing meningitis is uncommon and preventable by careful attention to aseptic technique.
3. Postdural puncture headache (PPH) is the most common post-LP complication.
   a. A smaller, atraumatic (pencil point) needle, parallel orientation to the dural fibers, and a paramedian approach—associated with a decreased risk of this complication. Typically develops within

72 hours and lasts 3 to 5 days and typically gets worse when upright compared with the supine position. Conservative treatment consisting of bed rest, hydration, and analgesics. If the symptoms are more severe, methylxanthines (caffeine or theophylline) may be successful in up to 85% of patients. If PPH persists or is unaffected, an epidural blood patch should be considered.

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15 Neurologic and Intracranial Pressure Monitoring

Raimis Matulionis

I. GENERAL PRINCIPLES

A. The brain uses more oxygen and glucose per 100 g of tissue than any large organ and is completely dependent on uninterrupted cerebral blood flow (CBF) (i.e., has no appreciable reserves of oxygen and glucose).

B. Clinical monitoring directed toward early detection and reversal of potentially dangerous conditions.

C. Neurologic monitoring falls into two distinct categories.

1. Electroencephalography (EEG) and evoked potentials (EPs): define a qualitative threshold consistent with the onset of cerebral ischemia.
2. Monitors of intracranial pressure (ICP), CBF, and cerebral metabolism: provide quantitative physiologic information.

D. Cerebral ischemia: defined as cerebral oxygen delivery (C_{DO_2}) insufficient to meet metabolic needs.

E. C_{DO_2} components: CBF, hemoglobin concentration, arterial hemoglobin saturation (Sa_{O_2}).

II. TECHNIQUES

A. Systemic monitoring.

1. Pulse oximetry (Sp_{O_2}) and blood pressure (BP) provide clues about the adequacy of global brain oxygenation.
2. Cerebral perfusion pressure (CPP = mean arterial pressure [MAP] – ICP) does not alter CBF over a range of pressures of approximately 50 to 150 mm Hg.
3. Pa_{CO_2} regulates cerebral vascular resistance over a range of 20 to 80 mm Hg.
4. CBF is acutely halved if Pa_{CO_2} is halved, and it is doubled if Pa_{CO_2} is doubled.
5. A decreasing arterial O_2 content (Ca_{O_2}), resulting from a decrease in hemoglobin or in Sa_{O_2}, normally causes CBF to increase.

B. Neurologic examination.

1. Neurologic examination quantifies three key characteristics: level of consciousness, focal brain dysfunction, and *trends* in neurologic function.
2. The Glasgow Coma Scale (GCS), originally developed as a prognostic tool, has become a quick, reproducible *estimate* of level of consciousness (Table 15-1).

TABLE 15-1 Glasgow Coma Score

Component	Response	Score
Eye opening	Spontaneously	4
	To verbal command	3
	To pain	2
	None	1
	Subtotal: 1–4	
Motor response (best extremity)	Obeys verbal command	6
	Localizes pain	5
	Exhibits flexion withdrawal	4
	Exhibits flexor response (decorticate posturing)	3
	Exhibits extensor response (decerebrate posturing)	2
	Shows no response (flaccid)	1
	Subtotal: 1–6	
Best verbal response	Oriented and converses	5
	Disoriented and converses	4
	Uses inappropriate words	3
	Makes incomprehensible sounds	2
	Has no verbal response	1
	Subtotal: 1–5	
	Total: 3–15	

C. Neuroimaging.

1. Cerebral computed tomography (CT): provides valuable prognostic information about ultimate neurologic outcome and about the risk of subsequent intracranial hypertension and brain structure but not function.
2. Magnetic resonance: provides better resolution than CT, but has limited use in acute trauma due to incompatibility with ferrous material, a frequent component of life support systems.

D. CBF monitoring.

1. Xenon 133 (^{133}Xe) clearance.
2. CT angiogram and perfusion: measures CBF and volume and mean transit time.
3. Transcranial Doppler flow velocity: used to identify vasospasm after traumatic and nontraumatic subarachnoid hemorrhage.
4. Thermal diffusion: The device determines CBF in one small region of cortex—could be a useful monitor of global CBF or of a specific region at risk of ischemia.

E. ICP monitoring.

1. ICP functions as the outflow pressure for the cerebral circulation.

2. Although CBF cannot be directly inferred from MAP and ICP, severe increases in ICP reduce both CPP and CBF.
3. ICP monitoring has been used for surveillance and goal-directed therapy.
4. The Brain Trauma Foundation and the American Association of Neurological Surgeons have published guidelines for the management of traumatic brain injury, including standards, guidelines, and options for the use of ICP monitoring.
   a. ICP monitoring is appropriate.
      i. In all salvageable patients with severe head injury (GCS score of 3 to 8 after resuscitation) and abnormal CT scan.
      ii. In patients with severe head injury and a normal CT scan if two or more of the following are noted at admission: age older than 40, unilateral or bilateral motor posturing, and systolic BP < 90 mm Hg.
      iii. Not monitoring ICP while treating for elevated ICP can be deleterious and result in poor outcome.
   b. Current data support 20 to 25 mm Hg as an upper threshold, above which treatment to lower ICP should generally be initiated.
   c. Devices are ranked based on their accuracy, stability, and ability to drain cerebrospinal fluid (CSF).
      i. Intraventricular devices: fluid-coupled catheter with an external strain gauge.
      ii. Intraventricular devices: microstrain gauge or fiber optic technology.
      iii. Parenchymal pressure transducer devices.
      iv. Subdural devices.
      v. Subarachnoid fluid–coupled devices.
      vi. Epidural devices.
   d. In addition to intracranial hypertension, other data that may prompt concern are the following.
      i. Widening of the ICP pulse (indicating diminishing intracranial compliance).
      ii. Plateau waves (cyclic increases in ICP, often 50 mm Hg or greater and lasting as long as 15 to 30 minutes).
   e. Complications of ICP monitoring include.
      i. Aggravation of cerebral edema.
      ii. Intracranial hemorrhage.
      iii. Cortical damage.
      iv. Infection.
      v. Device-related malfunction and injuries.

F. Brain oxygenation monitoring: With advances in technology, there is some early evidence that as adjunct to ICP monitoring it could be a useful tool for patient management and improved outcomes.

1. Jugular venous saturation monitoring: Episodes of desaturation (SjO_2 50% to 55%) are associated with worse outcomes.
2. Brain tissue oxygen tension (PbO_2): Low values of PbO_2 (10 to 15 mm Hg) and the extent of their duration (>30 minutes) are associated with high rates of mortality.

3. Near-infrared spectroscopy: determines the relative concentrations of oxygenated and deoxygenated hemoglobin in brain tissue.
4. Neurochemical monitoring: microdialysis technique—recovered dialysate can be analyzed for neurotransmitters or metabolic intermediates.

G. Electrophysiologic monitoring.

1. Used to detect potentially damaging cerebral hypoperfusion, isolated seizures, and status epilepticus and to define the depth or type of coma.
2. Has limited value as a precise diagnostic tool.
3. Quantitative EEG monitoring used to identify delayed ischemic deficits after subarachnoid hemorrhage, occasionally before clinical deterioration.
4. Sensory EPs, which include somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs), can be used as qualitative threshold monitors to detect severe neural ischemia by evaluating characteristic waveforms to specific stimuli.
5. Obliteration of EPs occurs only under conditions of profound cerebral ischemia or mechanical trauma. EP monitoring is one of the most specific ways in which to assess neurologic integrity.
6. EPs are insensitive to less severe deterioration of cerebral or spinal cord oxygen availability and are modified by sedatives, narcotics, and anesthetics.

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16 Percutaneous Suprapubic Cystostomy

Antonio Aponte-Feliciano, Jorge D. Yarzebski, and Kevin M. Dushay

I. ANATOMY

A. The urinary bladder is anterior and inferior to the peritoneal cavity and posterior to the pubic symphysis.

1. The bladder dome rises above the pubic symphysis when distended (Fig. 16-1).

B. The anterior–superior midline of the external surface of the urinary bladder is generally free of major blood vessels as well as the anterior abdominal wall.

1. Major arterial supply to anterior–superior surface is from internal iliac branches entering lateral walls of the bladder.

2. Venous drainage flows inferiorly and laterally to reach the internal iliac veins.

II. ALTERNATIVES TO PERCUTANEOUS SUPRAPUBIC CYSTOSTOMY

A. Urethral catheterization.

III. INDICATIONS

A. Unsuccessful urethral catheterization in the setting of

1. Acute or chronic urinary retention.

2. Need for accurate urinary output monitoring.

3. Prostatic hyperplasia, cancer, or prior prostate surgery.

4. Loss of or threat to skin integrity due to urinary incontinence.

B. Inability to tolerate urethral catheter.

1. Following prostate or pelvic surgery, urethral pain, excoriation, necrosis, dementia/delirium causing patient to repeatedly remove catheter.

C. Urethral disruption from pelvic trauma/fracture.

D. Bladder drainage in the presence of severe infection: urethral, prostatic, or epididymal.

E. Neurogenic bladder.

F. Spinal cord injury patients.

1. May be easier for patient or caregiver.

2. May reduce frequency of urinary tract infections.

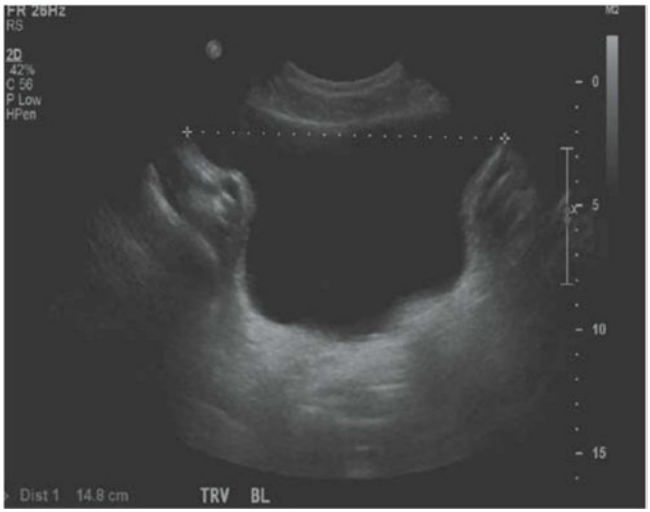

Figure 16-1. Ultrasound view of a distended bladder above the symphysis pubis.

IV. CONTRAINDICATIONS

A. Nonpalpable bladder, bowel loops over the anterior bladder wall on sonographic evaluation.
B. Previous lower abdominal surgery.
C. Bladder carcinoma.
D. Coagulopathy, anticoagulant, or antiplatelet medication administration is a relative contraindication.
E. Lower abdominal wall infection.

V. PROCEDURE

A. Obtain informed consent from the patient, health care proxy, or legal guardian and perform a time-out and follow the universal precautions protocol.
B. Equipment.

1. Two main types of devices.
a. Catheter over introducer needle or obturator.
b. Sheath over needle or introducer, through which catheter is inserted.

C. Technique (see Video 18-1).

1. Common procedure.
a. Localize the bladder by palpation and/or by ultrasound to evaluate, locate, and decrease the risk of trauma to adjacent structures.
b. Familiarize yourself with the supplies; the kit may not include prep, lidocaine, catheter, or collection system.
c. Follow aseptic precautions (mask, cap, eyeshields, gown, sterile gloves, full body drapes).

d. Clip hair from the suprapubic area (if necessary); position the patient in Trendelenburg position; chlorhexidine prep, drape, lay out equipment, and check catheter and the balloon (if present) for integrity.

e. Inject 1% lidocaine and make a midline skin wheal 2 to 4 cm above pubic symphysis; anesthetize tract perpendicular to body axis or angled 20 degrees caudally through subcutaneous tissue and rectus abdominis fascia using finder/introducer needle until bladder entry confirmed by aspiration of urine; then use scalpel to make stab wound along axis of needle.

2. Catheter over trocar technique.

a. Withdraw finder needle; holding device near skin surface, insert it along prepared path until urine aspirated.

b. Advance the device slightly and slide catheter into bladder while fixing trocar in place.

c. Then remove trocar and secure catheter in position.

3. Seldinger technique.

a. Remove syringe.

b. Pass guidewire through introducer needle to indicator mark.

c. Withdraw needle and pass the dilator(s) over the guidewire holding the dilator close to the skin until the introducer with preloaded catheter or sheath can be inserted into bladder.

d. Pinch the sheath as the guidewire and introducer are withdrawn to avoid urine leakage.

e. Pass catheter through sheath until urine is obtained, then deploy the anchor/ balloon, and then withdraw and peel sheath away keeping catheter in place; secure catheter.

4. Catheter with internal fixation device.

a. Gently withdraw until resistance felt.

b. Advance the assembly 2 cm before securing to avoid bladder spasms.

VI. POSTPROCEDURE CONSIDERATIONS

A. Complications.

1. Hematuria—most common.

2. Bladder spasms also common.

a. Can use any antispasmodic.

i. Stop antispasmodics before suprapubic tube removal to avoid urinary retention.

3. Hemorrhage.

4. Bowel, rectal, uterine, or vaginal injury.

5. Bladder perforation.

6. Ureteral catheterization.

7. Catheter dislodgement or kinking.

8. Infection (i.e., cellulitis, deep wound infection, cystitis, pyelonephritis, and bacteremia).

9. Postobstructive diuresis.

10. Hypotension.

11. Retained catheter or guidewire fragment.

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17 Aspiration of Joints

Harvey S. Reich

I. GENERAL PRINCIPLES

A. Overview.

1. Arthrocentesis involves the introduction of a needle into a joint space to remove synovial fluid.
2. It is an essential diagnostic technique for the evaluation of arthritis of unknown cause.
3. The presentation of conditions such as septic arthritis and crystalline arthritis may be similar, yet treatment may be different.
4. Arthrocentesis and synovial fluid analysis are important for accurate diagnosis.
5. Arthritis can involve a single joint (monoarthritis) or multiple joints (oligoarthritis).

II. INDICATIONS

A. Principles.

1. Arthrocentesis is performed for both diagnostic and therapeutic reasons.
2. In the intensive care unit, arthrocentesis is most commonly performed to rule out septic arthritis in a patient with acute monoarthritis or oligoarthritis.
3. Before performing arthrocentesis, one must be certain that true joint space inflammation with effusion is present rather than a periarticular inflammatory process, such as bursitis, tendinitis, or cellulitis.
4. In the knee, the presence of an effusion may be confirmed by the bulge test or patella tap.
   a. Bulge test: Milk fluid from the suprapatellar pouch into the joint, slide the hand down the lateral aspect of the joint line, and watch for a bulge medial to the joint.
   b. Patellar tap: Apply pressure to the suprapatellar pouch while tapping the patella against the femur to determine if the patella is ballottable, which indicates an effusion.
5. Arthrocentesis with ultrasound guidance for evaluation of the joint and surrounding soft tissues can be performed at the bedside to assess for joint fluid, bursal fluid, or other soft tissue fluid collections such as an abscess. This can allow evaluation of bursal or soft tissue collections that may go undetected by blind aspiration.

6. Arthrocentesis may also be used therapeutically, as in the serial aspiration of a septic joint for drainage and monitoring of the response to treatment.
7. Arthrocentesis allows for therapeutic injection of corticosteroid preparations into the joint space for treatment of various forms of inflammatory and noninflammatory arthritis.

B. Etiology of inflammatory arthritis.

1. Rheumatoid arthritis.
2. Spondyloarthropathies.
   a. Psoriatic arthritis.
   b. Seronegative spondyloarthropathy.
   c. Ankylosing spondylitis.
   d. Ulcerative colitis/regional enteritis.
3. Crystal-induced arthritis.
   a. Monosodium urate (gout).
   b. Calcium pyrophosphate dehydrate (pseudogout).
   c. Hydroxyapatite.
4. Infectious arthritis.
   a. Bacterial.
   b. Mycobacterial.
   c. Fungal.
5. Connective tissue diseases.
   a. Systemic lupus erythematosus.
   b. Vasculitis.
   c. Scleroderma.
   d. Polymyositis.
6. Hypersensitivity.
   a. Serum sickness.

C. Etiology of noninflammatory arthritis.

1. Osteoarthritis.
2. Trauma/internal derangement.
3. Avascular necrosis.
4. Hemarthrosis.
5. Malignancy.
6. Benign tumors.
   a. Osteochondroma.
   b. Pigmented villonodular synovitis.

D. Contraindications.

1. Absolute contraindications to arthrocentesis include infection of the overlying skin or periarticular structures and severe coagulopathy.
2. If septic arthritis is suspected in the presence of severe coagulopathy, efforts to correct the bleeding diathesis should be made before joint aspiration.
3. Although known bacteremia is a contraindication to arthrocentesis given the potential for joint space seeding, joint aspiration is

nonetheless indicated if septic arthritis is the presumed source of the bacteremia.

4. Articular damage and instability constitute relative contraindications to arthrocentesis.

III. PROCEDURE

A. Arthrocentesis equipment.

1. Skin preparation.
   a. Two percent chlorhexidine and seventy percent isopropyl combination antiseptic or equivalent (ten percent povidone–iodine solution should be used only if the patient has a sensitivity to chlorhexidine).
2. Local anesthesia.
   a. 1% Lidocaine; 25-gauge, 1-in. needle; 22-gauge, 1.5-in. needle; and 5-mL syringe.
   b. Sterile sponge/cloth.
3. Arthrocentesis.
   a. Sterile gloves.
   b. 10- to 60-mL syringe (depending on size of effusion).
   c. 18- to 20-gauge, 1.5-in. needle.
   d. Sterile sponge/cloth.
   e. Adhesive bandage (Band-Aid).
4. Collection.
   a. Fifteen milliliters in an anticoagulated tube.
   b. Sterile tubes for routine Gram stain and cultures.
   c. Slide, cover slip.

B. Technique.

1. Joint aspiration requires knowledge of the relevant joint and periarticular anatomy and strict adherence to aseptic technique.
2. Joints other than the knee should be aspirated by an appropriate specialist.
3. Aspiration of some joints, such as the hip or sacroiliac joints, may require fluoroscopic, ultrasound, or computed tomographic guidance.
4. Confirm the presence of an effusion with the patient supine and the knee extended.
5. The superior and inferior borders of the patella are landmarks for needle placement.
6. Entry should be halfway between these borders just inferior to the undersurface of the patella, from either a medial or lateral approach, the former being more commonly used and preferable with small effusions.
7. Cleanse the area with a chlorhexidine–isopropyl alcohol antiseptic solution. Allow the area to dry.
8. Perform a time-out confirming the correct side and follow the universal precautions protocol.

9. Local anesthesia can be achieved with infiltration of local anesthetic solution (e.g., 1% lidocaine) into the subcutaneous and deeper tissues.
10. To enter the knee joint, use an 18- to 20-gauge, 1.5-in. needle with a sterile 20- to 60-mL syringe.
11. Use a quick thrust through skin and capsule.
12. Avoid periosteal bone to minimize pain.
13. Aspirate fluid to fill the syringe. If the fluid appears purulent or hemorrhagic, try to tap the joint dry.
14. Drainage of large effusions may require additional syringes, which may be exchanged for the original one while leaving the needle in place.
15. When the fluid has been obtained, the needle is removed, and pressure is applied to the puncture site with sterile gauze.
16. Apply an adhesive bandage after cleaning the area with alcohol. Apply prolonged pressure if the patient has a bleeding diathesis of any type.
17. Document the amount, color, clarity, and viscosity of the fluid. Send the fluid for cell count with differential, Gram stain, and routine culture; cultures for gonococcus, mycobacteria, and fungi, if indicated; and polarized microscopic examination for crystal analysis.
18. Anticoagulated tubes are needed for accurate assessment of fluid for cell count and crystal analysis.
19. Other tests, including glucose and complement levels, are generally not helpful.

C. Synovial fluid analysis (Table 17-1).

1. Synovial fluid is divided into noninflammatory versus inflammatory types based on the total nucleated cell count.
2. A white blood cell (WBC) count of 2,000/mm^3 defines an inflammatory fluid.

TABLE 17-1 Joint Fluid Characteristics

	Normal	Noninflammatory	Inflammatory	Septic
Color	Clear	Yellow	Yellow or opalescent	Variable; may be purulent
Clarity	Transparent	Transparent	Transparent	Opaque
Viscosity	Very high	High	Low	Typically low
Mucin clot	Firm	Firm	Friable	Friable
WBC/mm^3	<200	200–2,000	2,000–100,000	>50,000, often >100,000
PNM%	<25	<25	>50	>75
Culture	Negative	Negative	Negative	Usually positive

D. Color.

1. Normal synovial fluid is colorless.
2. Noninflammatory and inflammatory joint fluid has a yellow hue.
3. Septic effusions often appear whitish to frankly purulent.
4. Hemorrhagic effusions appear red or brown.
5. A repeated aspiration from an alternate site may be required if there is a question of a traumatic tap.
6. The hematocrit in a hemorrhagic effusion is typically lower than that of a peripheral sample and is equal to it in the case of traumatic tap.

E. Clarity.

1. The clarity of the synovial fluid depends on the amount of cellular or particulate matter within it.
2. On the basis of how well, if at all, black print on a white background can be read through a glass tube filled with synovial fluid, the fluid is categorized as being transparent, translucent, or opaque.

F. Viscosity.

1. The viscosity of synovial fluid is a measure of the hyaluronic acid content.
2. Degradative enzymes such as hyaluronidase are produced in inflammatory conditions resulting in a thinner, less viscous fluid.
3. The string sign is a bedside measure of viscosity.
4. Normal synovial fluid forms at least a 6-cm continuous string when a drop of fluid is allowed to fall from the needle or syringe.
5. Inflammatory fluid drips and will not form a string.
6. The mucin clot, another measure of viscosity, is a test performed by mixing several drops of synovial fluid in 5% acetic acid.
7. A good, tenacious mucin clot forms with normal, noninflammatory fluid but not with an inflammatory sample.

G. Cell count and differential.

1. The cell count should be obtained as soon as possible after arthrocentesis to avoid a falsely low WBC count caused by delayed analysis.
2. Viscous fluid with much debris may give erroneous results with automated counters, thereby making a manual count more accurate in these circumstances.
3. The total WBC count and polymorphonuclear (PMN) cell count increase with infection and inflammation.
4. Septic fluid typically has a differential of >75% PMN cells.

H. Crystals.

1. As with the cell count, crystal analysis should be performed as soon as possible after arthrocentesis for optimal diagnostic yield.
2. Fluid is examined for crystals using a compensated polarized light microscope.
3. The presence of intracellular monosodium urate or calcium pyrophosphate dihydrate (CPPD) crystals confirms the diagnosis of gout or pseudogout, respectively.

4. Monosodium urate crystals are usually needle shaped, are negatively birefringent, and appear yellow when oriented parallel to the compensator axis.
5. CPPD crystals typically are smaller and rhomboid, weakly positively birefringent, and appear blue when parallel to the plan of reference.
6. If the fluid cannot be examined immediately, it should be refrigerated to preserve the crystals.
7. Even when crystals are found in a sample, infection must be considered, because crystals can occur concomitantly with a septic joint.

I. Gram stain and culture.

1. The Gram stain is performed as with other body fluids.
2. Synovial fluid should routinely be cultured for aerobic and anaerobic organisms. Additional cultures for fungi, mycobacteria, and disseminated gonorrhea should be sent if clinically indicated.

IV. POSTPROCEDURE CONSIDERATIONS

A. Complications.

1. The major complications of arthrocentesis are bleeding and iatrogenically induced infection.
2. These complications are exceedingly rare with strict adherence to aseptic technique and with correction of significant coagulopathy before joint aspiration.
3. Direct cartilaginous damage by the needle is difficult to quantitate and likely is minimized by avoidance of excessive needle movement or complete drainage of the joint, as well as avoiding advancement of the needle any deeper than needed to obtain fluid.

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18 Anesthesia for Bedside Procedures

Nathanael A. Slater and J. Matthias Walz

I. GENERAL PRINCIPLES

A. Managing pain in critical illness.

1. Anesthesia for bedside procedures in the intensive care unit (ICU) is accomplished with total intravenous anesthesia (TIVA).
2. Selecting the proper dose of an analgesic to administer is challenging because of
   a. Difficulty in assessing the effectiveness of pain relief (delirium, obtundation, endotracheal intubation).
   b. Pharmacokinetic (PK) differences between critically ill and other patients.
   c. Physiologic changes associated with aging (decrease in lean body mass, increase in volume of distribution of lipid-soluble drugs, decrease in drug clearance rates, increased sensitivity to hypnotics and analgesics).

B. PK considerations.

1. PK behavior in critically ill patients is unlike that in normal subjects for the following reasons (see also Dershwitz 2012, in Suggested Readings, for more detail).
   a. ICU patients frequently have renal and/or hepatic dysfunction; therefore, drug metabolism and elimination may be significantly impaired.
   b. Hypoalbuminemia, common in critical illness, can decrease protein binding and increase free (active) drug concentration.

II. INDICATIONS

A. Selection of agent.

1. Procedures performed in the ICU can be differentiated according to their associated levels of discomfort.
   a. Mild to moderately uncomfortable (esophagogastroscopy, paracentesis).
   b. Moderately to severely uncomfortable (endotracheal intubation, thoracostomy, flexible bronchoscopy).
   c. Extremely painful (rigid bronchoscopy, orthopedic manipulations, tracheotomy).
2. Specific disease states should be considered so that safety and effectiveness are maximized.
   a. Head trauma.

i. Effective yet brief anesthesia is desirable so that the capacity to assess neurologic status is not lost for extended periods.
ii. The technique should not adversely affect cerebral perfusion pressure.
iii. If the effects of the medications dissipate too rapidly, undesirable episodes of agitation and increased intracranial pressure (ICP) may occur.

b. Coronary artery disease: Sufficient analgesia is necessary during and after invasive procedures to minimize tachycardia (which is a major determinant of ischemia) and reduce plasma catecholamine and stress hormone levels.

c. Renal or hepatic failure.
i. The risk of an adverse drug reaction is at least three times higher in patients with azotemia compared to those with normal renal function.
ii. Liver failure alters the volume of distribution of many drugs by impairing synthesis of albumin and α_1-acid glycoprotein.
iii. Reductions in hepatic blood flow and hepatic enzyme activity decrease drug clearance rates.

III. PROCEDURE

A. Hypnotics: The characteristics of commonly used hypnotics are listed in Table 18-1.

1. Propofol.

a. Propofol is an extremely popular hypnotic agent for the following reasons.
i. It is readily titratable and has more rapid onset and offset kinetics than midazolam.
ii. The rapid recovery of neurologic status makes propofol a good sedative in ICU patients, especially those with head trauma.
iii. Spontaneously breathing patients anesthetized with propofol may maintain normal end-tidal carbon dioxide values during minor surgical procedures.

b. Maintenance infusion rates of 100 to 200 μg/kg/min are adequate in younger subjects, which should be reduced by 20% to 50% in elderly individuals.

c. Adverse effects of propofol administration include
i. Hypotension from depressed ventricular systolic function and/or decreased afterload.
ii. In patients with coronary artery disease, propofol administration may be associated with a reduction in coronary perfusion pressure.
iii. The emulsion used as the vehicle for propofol supports bacterial growth; iatrogenic contamination leading to septic shock is possible.
iv. Hyperlipidemia with prolonged infusions can occur, particularly in infants and small children.

TABLE 18-1 Characteristics of Intravenous Hypnotic Agents

	Propofol	Etomidate	Ketamine	Midazolam	Dexmedetomidine
Bolus dose (mg/kg)	1–2	0.2–0.3	1–2	0.05–0.1	0.5–1 μg/kg over 10 min
Onset	Fast	Fast	Fast	**Intermediate**	**Intermediate**
Duration	Short	Short	Intermediate	Intermediate	Short
Cardiovascular effects	↓	**None**	↑	Minimal	Moderate ↓
Respiratory effects	↓	↓	**Minimal**	↓	**Minimal**
Analgesia	None	None	**Profound**	None	Minimal
Amnesia	Mild	Mild	**Profound**	**Profound**	**Profound**

↓, decrease; ↑, increase.
The listed doses should be reduced 50% in elderly patients. Entries in bold type indicate noteworthy differences among the drugs.

2. **Etomidate.**
   - **a.** Etomidate has onset and offset PK characteristics similar to those of propofol and lacks significant effects on myocardial contractility (even in the setting of cardiomyopathy).
   - **b.** Etomidate depresses cerebral oxygen metabolism and blood flow in a dose-dependent manner without changing the intracranial volume–pressure relationship.
   - **c.** Etomidate is particularly useful in patients with
     - **i.** Hypovolemia.
     - **ii.** Multiple trauma victims with closed head injury.
     - **iii.** Patients with low ejection fraction, severe aortic stenosis, left main coronary artery disease, or severe cerebrovascular disease.
   - **d.** Adrenal suppression can occur.
     - **i.** Prolonged infusion is not recommended because of adrenocortical suppression.
     - **ii.** A single induction dose of etomidate may increase mortality in patients with established or evolving septic shock.
3. **Ketamine.**
   - **a.** Ketamine is unique among the hypnotic agents in that it has analgesic, sedative, and amnestic effects.
   - **b.** Ketamine has a slower onset and offset as compared to propofol or etomidate following intravenous (IV) infusion, and stimulates the cardiovascular system (i.e., raises heart rate and blood pressure by direct stimulation of the central nervous system [CNS]).
   - **c.** Ketamine may be safer than other hypnotics or opioids in nonintubated patients because it depresses airway reflexes and respiratory drive to a lesser degree.
   - **d.** In the usual dosage, ketamine decreases airway resistance.

e. The administration of ketamine can be associated with disorientation, sensory and perceptual illusions, and vivid dreams; these effects have been termed *emergence phenomena*. To avoid emergence phenomena after ketamine administration, pretreatment or concurrent treatment with a benzodiazepine or propofol should be considered.

f. The combination of ketamine with a benzodiazepines and/or an opioid is useful in patients with coronary artery disease to avoid myocardial ischemia (the use of ketamine alone increases myocardial oxygen consumption).

g. Ketamine is relatively contraindicated in patients with increased ICP.

4. Midazolam.

a. Administration of midazolam produces anxiolysis, amnesia, and relaxation of skeletal muscle (ideally suited for brief, relatively painless procedures as well as for prolonged sedation).

b. Midazolam is highly (95%) protein bound, and recovery is prolonged in obese and elderly patients and after continuous infusion because it accumulates significantly.

c. In patients with renal failure, active conjugated metabolites of midazolam may accumulate and delay recovery.

d. Midazolam (0.15 mg/kg IV) causes respiratory depression and blunts the ventilatory response to hypoxia.

e. Midazolam has a stable cardiovascular profile and causes dose-dependent reductions in cerebral metabolic rate and cerebral blood flow.

B. Opioids.

1. Opioids blunt pain by

a. Inhibiting pain processing by the neurons of the dorsal horn of the spinal cord.

b. Decreasing transmission of pain by activating descending inhibitory pathways in the brainstem.

c. Altering the emotional response to pain by actions on the limbic cortex.

2. Morphine.

a. Morphine is an agonist at μ, κ, and δ receptors.

b. Morphine causes significant histamine release after IV bolus injection.

c. Adverse effects of morphine include

i. Gastrointestinal.

(a) Constipation, nausea, and/or vomiting.

(b) Reduced gastric emptying and bowel motility.

ii. Cardiovascular: hypotension, especially if it is given rapidly (i.e., 5 to 10 mg/min).

iii. Respiratory.

(a) Morphine decreases the ventilatory response to CO_2 and hypoxia.

(b) Exaggerated ventilatory depression in patients with renal failure is possible because of the active metabolite, morphine-6-glucuronide.

3. **Fentanyl and related drugs.**
   a. Fentanyl, alfentanil, sufentanil, and remifentanil enter and leave the CNS much more rapidly than morphine (much faster onset of effect after IV administration).
   b. They are selective μ-opioid receptors agonists (the only significant difference among these agents is their PK behavior).
   c. Fentanyl may be useful when given by intermittent bolus injection (50 to 100 μg), but when given by infusion its duration becomes prolonged.
   d. Remifentanil owes its extremely short duration to rapid metabolism by tissue esterases (primarily in skeletal muscle); its PK behavior is unchanged in the presence of severe hepatic or renal failure.
   e. Sufentanil infusion for TIVA may be initiated with a 0.5 to 1.5 μg/kg bolus followed by an infusion at 0.01 to 0.03 μg/kg/min.
   f. Remifentanil infusion for TIVA may be initiated with a 0.5 to 1 μg/kg bolus followed by an infusion at 0.25 to 1 μg/kg/min.
   g. Adverse effects can include hypotension when administered as a bolus, increases in ICP and adverse effects on cerebral perfusion pressure (fentanyl and sufentanil), and chest wall rigidity with large doses (fentanyl).

C. Dexmedetomidine.

1. Dexmedetomidine is an α-2 agonist, which provides sedation and sympatholysis and can be used as an analgesic adjunct for invasive procedures in the ICU. The drug is FDA approved for short-term administration (96 hours) as a continuous infusion of 0.2 to 0.7 μg/kg/h.
   a. Dexmedetomidine is administered as follows.
      i. If a bolus dose is required, the dose range is 0.5 to 1 μg/kg given over 10 minutes, followed by an infusion of 0.2 to 0.7 μg/kg/h.
      ii. Higher (off-label) doses up to 1.4 μg/kg/h (some up to 2.5 μg/kg/h) have been reported in the literature to be associated with increased risk of adverse effects such as hypotension and bradycardia in the higher dose range.
2. Potential uses in the ICU include sedation for bronchoscopy, awake fiberoptic intubation, and ameliorating agitation due to alcohol withdrawal or head injury.
3. Dexmedetomidine produces little respiratory depression but can cause bradycardia and hypotension.

D. Neuromuscular blocking agents.

1. **Succinylcholine.**
   a. Succinylcholine 1 mg/kg IV will result in excellent intubating conditions in less than a minute. It is the drug of choice when the airway must be secured quickly (full stomach or symptomatic gastroesophageal reflux) unless there are contraindications.
   b. Succinylcholine may trigger malignant hyperthermia in genetically susceptible persons.
   c. Succinylcholine may cause a malignant rise in the extracellular potassium concentration in patients with major acute burns, upper or lower motor neuron lesions, prolonged immobility, massive crush injuries, and various myopathies.

2. **Nondepolarizing neuromuscular blocking (NMB) agents.**
   a. Vecuronium (0.1 mg/kg), rocuronium (0.6 to 1.2 mg/kg), and cisatracurium (0.1 to 0.2 mg/kg) are used when succinylcholine is contraindicated and are essentially devoid of cardiovascular effects.
   b. NMB agents may cause muscle weakness persisting for months afterward: Risk factors include concomitant glucocorticoid therapy or prolonged NMB.

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19 Routine and Cardiorespiratory Monitoring in the Intensive Care Unit

Gisela I. Banauch and Eric Cucchi

I. TEMPERATURE

A. General principles.

1. Estimate core temperature that is independent of ambient fluctuations because of hypothalamic regulation.

B. Indications.

1. Indications are extensive and include infection, temperature dysregulation syndromes (autonomic dysfunction, neuroleptic malignant syndrome, malignant hyperthermia, endocrine syndromes), certain toxidromes (anticholinergic, serotonin syndrome), and environmental causes of temperature dysregulation.

C. Procedure.

1. Measure at least every 4 hours, continuously when <36°C or >39°C, or temperature-altering interventions (cooling blanket, active rewarming) are applied. Probes in the mouth, axilla, auditory canal, or on the skin overlying the temporal artery allow intermittent monitoring. Probes in the pulmonary artery, rectum, esophagus, or bladder allow continuous monitoring.

D. Postprocedure considerations.

1. Rectal site can transmit resistant enteral bacteria. Axillary temperature is considered 1°F cooler than core temperature.

II. ARTERIAL PRESSURE

A. General principles.

1. Assure adequate perfusion pressure for sufficient substrate/oxygen delivery and metabolic waste/carbon dioxide (CO_2) removal.
   - **a. Arterial catheter.**
     - **i.** Allows continuous monitoring. A fluid column continuously transmits arterial pressure to a transducer, where it is converted into electrical signals through diaphragm deformation–induced resistance changes in a Wheatstone bridge.
   - **b. Automated oscillometric monitor.**
     - **i.** Allows intermittent monitoring. Analyzes magnitude/shape of arterial pressure oscillations with intermittent, controlled, slow blood pressure cuff inflation/deflation.

B. Indications.

1. **Arterial catheter.**
   a. Indications for continuous monitoring are patients who are on vasoactive medications or who require frequent blood gas analyses.
2. **Automated oscillometric monitor.**
   a. Indications for intermittent monitoring are patients at risk for hypo- or hypertension, which includes all patients admitted to an intensive care unit.

C. Procedure.

1. **Arterial catheter.**
   a. Seldinger technique is used for insertions at the radial, femoral, and axillary sites. Once the catheter is placed, it is connected to the fluid column that is in specialized pressure tubing. The system is zeroed at the level of the right atrium.
2. **Automated oscillometric monitor.**
   a. Cuff bladder width should equal 40%, and the length should equal/exceed 60% of extremity circumference. The cuff bladder is inflated until the distal pulse is obliterated. Air is slowly released from the cuff. When systolic pressure is reached, blood flow begins and is detected by the monitor as arterial wall vibrations. Arterial vibrations stop when diastolic pressure is reached.

D. Postprocedure considerations.

1. **Arterial catheter.**
   a. Complications include distal vessel occlusion, hemorrhage, and infection.
   b. Erroneously high pressures from small air bubbles/heart rates close to transducer system's resonant frequency (overshoot).
   c. Erroneously low pressures from large air bubbles and catheter thrombus/heart rates above transducer system's resonant frequency (damping).
2. **Automated oscillometric monitor.**
   a. Intermittent measurements do not reflect rapidly changing hemodynamics.
   b. Inadequately sized cuffs (width/length) overestimate.
   c. Poor correlation with intra-arterial values at pressure extremes.
   d. Complications include distal limb ischemia and venous stasis with prolonged/frequent cuff inflation or deflation failure; do not perform on limbs with compromised arterial/venous/lymphatic circulation.
   e. Mean arterial pressure is a more reliable indicator of tissue perfusion than systolic and diastolic pressures.

III. ELECTROCARDIOGRAPHY

A. General principles.

1. Monitor endogenous cardiac electrical impulses to detect malignant arrhythmias or changes in electrical morphology as a result of structural

damage to the myocardial tissue. Computerized arrhythmia detection is based on heart rate variability, electrocardiogram (ECG) intervals/segment durations, and ECG morphology.

B. Indications.

1. All critically ill patients should have an ECG as a baseline upon admission. Other indications are a high likelihood of malignant arrhythmia and/or cardiac ischemia.

C. Postprocedure considerations.

1. Artifacts arise from muscle activity or poor transmission (obesity, poor skin preparation, improperly positioned electrodes).

IV. RESPIRATORY MONITORING

A. General principles.

1. Assure adequate gas exchange.
2. **Impedance pneumography.**
   a. Measures thoracic impedance changes due to respiration-induced alterations in thoracic geometry and thus quantifies respiratory rate.
3. **Mechanical ventilator.**
   a. Measures inhaled/exhaled airflow versus time; derives respiratory rates, tidal volumes, and minute ventilation.
4. **Pulse oximetry.**
   a. Uses photoplethysmography to measure the difference in light absorption spectra of oxygenated/deoxygenated hemoglobin across pulsatile tissue bed over time; calculates absorption ratio change over time, which estimates arterial oxygen saturation.

B. Postprocedure considerations.

1. **Impedance pneumography.**
   a. Imprecise at respiratory rate extremes and with physical motion.
2. **Mechanical ventilator.**
   a. Moisture on pneumotachograph overestimates flow/volume.
   b. Circuit leaks over- or underestimate respiratory rate and flow/volume.
3. **Pulse oximetry.**
   a. Erroneous measurements from poor tissue perfusion (low cardiac output [CO], high systemic vascular resistance, hypothermia, vasoconstrictors, hypovolemia, hypotension).
   b. Falsely low measurements from methylene blue and other intravascular dyes.
   c. Falsely elevated measurements from carboxy/methemoglobinemia.
   d. Falsely low measurements in severe tricuspid insufficiency (venous regurgitation into capillaries results in pulsatile venous flow).
   e. Forehead probes less reliable because they may include venous signals; earlobe probes less prone to artifact.

V. CAPNOGRAPHY

A. General principles.

1. Measures and displays expired partial pressure of carbon dioxide ($ETCO_2$) by infrared absorbance or mass spectrometry.

B. Indications.

1. Verification of artificial airway placement.
2. Detection of extubation.
3. Detection return of spontaneous circulation after cardiac arrest.

C. Procedure.

1. Airway gases can be sampled by sidestream or mainstream techniques during mechanical ventilation.

D. Postprocedure considerations.

1. Changes in dead space will affect end-tidal PCO_2 (last 20% of exhalation).
2. Changes on the shape of the waveform can indicate resistance to airflow (e.g., bronchospasm), cardiogenic oscillations, or attempts at spontaneous breathing during controlled mechanical ventilation.

VI. CARDIAC OUTPUT MEASUREMENT

A. Thermodilution (see Chapter 4).
B. Esophageal Doppler (Fig. 19-1).

1. General principles.
   a. Doppler probe placed in esophagus uses Doppler shift principle to measure velocity of blood in descending aorta.
   b. Multiplying the cross-sectional area of the aorta by the velocity will yield flow (stroke volume).
      i. Algorithms exist for estimating cross-sectional aortic area.
      ii. Other probes have an ultrasound, which can be used to measure the area.
   c. Flow time corrected (FT_c) correlates with preload.
   d. Peak velocity correlates with contractility.
2. Indications: monitoring of hemodynamic variables including CO in unstable patients.
3. Procedure.
   a. Insert probe either through mouth or nose and into the esophagus with the probe directed posteriorly toward the descending aorta.
   b. Position the probe to obtain the best waveform on the monitor (Fig. 19-1).
4. Postprocedure considerations.
   a. Probe may be left in place for extended period of time.
   b. Probe will likely need to be repositioned or refocused between measurement to obtain optimal waveform.

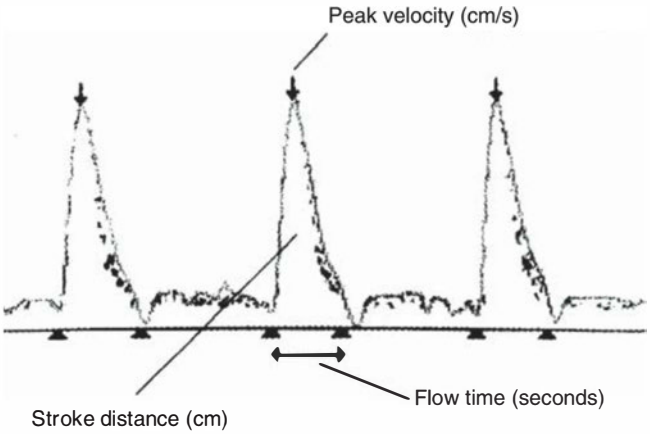

Figure 19-1. Esophageal Doppler flow-velocity waveform. (Adapted from Marik PE. Pulmonary artery catheterization and esophageal Doppler monitoring in the ICU. *Chest* 1999;116:1085–1091.)

C. Pulse contour analysis.

1. General principles.
- **a.** Uses an algorithm and invasively measured arterial blood pressure to derive a continuous CO.
- **b.** All but one system requires CO calibration with either a transpulmonary thermodilution technique or lithium dilution technique.
- **c.** Changes in arterial impedance will necessitate a repeat calibration.

2. Indications: monitoring of hemodynamic variables including CO in unstable patients.

3. Procedure.
- **a.** Insertion of radial or femoral arterial catheter (see Chapter 3) and central venous catheter (CVC, see Chapter 2).
- **b.** The arterial catheter is attached to the proprietary monitoring equipment that will measure the CO.
- **c.** The CVC is required for transpulmonary CO measurement (which is needed for the calibration).

4. Postprocedure considerations.
- **a.** Stroke volume variation can be used to assess fluid responsiveness in mechanically ventilated patients but only when tidal volumes of >8 ml/kg are used.
- **b.** Accuracy of systems that do not use CO calibration has been brought into question.
- **c.** Accuracy of all of these systems during large changes in blood pressure and use of vasoconstrictors is questionable.

D. Partial carbon dioxide rebreathing method.

1. General principles.
   a. Use of a device that allows for partial rebreathing of exhaled gas.
   b. CO is calculated by changes in carbon dioxide excretion and values of end-tidal carbon dioxide during normal and partial rebreathing periods.
2. Indications: monitoring of CO in unstable patients.
3. Procedure.
   a. Requires intubated patient.
   b. Apparatus is attached to the endotracheal tube and airway circuit of the patient.
4. Postprocedure considerations.
   a. Accuracy affected by tidal volume.
   b. Unclear if it is safe to use in patients with hypercapnia or elevated intracranial pressure.

E. Bioreactance.

1. General principles.
   a. Measures bioreactance or phase shift in voltage across the thorax.
   b. Phase shifts occur due to pulsatile flow (mostly from the aorta).
   c. Entirely noninvasive.
2. Indications: monitoring of CO in unstable patients.
3. Procedure.
   a. Four dual electrodes are placed on the chest—two on each side—and attached to monitor.
   b. Transmits high-frequency sine waves and measures voltage changes.
4. Postprocedure considerations.
   a. Electrocautery interferes with the signal.
   b. Accurate with ventricular and atrial arrhythmias.
   c. Compares favorably with thermodilution determined CO.

VII. URINE OUTPUT MONITORING

A. General principles.

1. Reflects kidney perfusion and thus is often used as marker of global tissue perfusion.

B. Indications.

1. Assess/monitor for decreased tissue perfusion and/or acute kidney injury in critically ill patients including those with severe burn injuries, shock states, or hemorrhage.

C. Procedure.

1. Continuous monitoring requires bladder catheterization.
2. Intermittent monitoring requires urine collection.

D. Postprocedure considerations.

1. Indwelling bladder catheters confer a significant risk of infection as well as of lower urinary tract trauma.

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20 Echocardiography in the Intensive Care Unit

Dennis A. Tighe, Dinesh Chandok†, and Gerard P. Aurigemma

I. GENERAL PRINCIPLES

A. Echocardiography is frequently performed in critically ill patients. The major advantages of this diagnostic technique are its portability, lack of patient exposure to ionizing radiation and iodinated contrast, ability to provide real-time structural and functional (hemodynamic) information, and suitability for serial performance.

B. Structural and functional information is provided by transmitting ultrasound (US) energy (2 to 10 MHz) from the echocardiograph and receiving signals returning from the cardiac structures to create real-time two- (2D) and three-dimensional (3D) images of the heart.

C. Using the Doppler principle, reflected US energy is used to determine the velocity and direction of flowing blood in the heart and great vessels providing information about the hemodynamic effects of stenotic and regurgitant valve lesions. In addition, Doppler echocardiography provides information about filling pressures, stroke volumes, and pulmonary artery systolic pressures. Peak instantaneous pressure gradients (P) are estimated by measuring the peak flow velocity (V) and application of the modified Bernoulli equation, $P = 4V^2$. Color-flow Doppler provides a spatial velocity map of abnormal flow within the heart and great vessels; it is most useful to estimate the degree of valvular regurgitation and identifying turbulent blood flow. Tissue Doppler imaging adds to the ability to estimate left heart filling pressures.

D. A complete examination includes information provided by the 2D, Doppler, color-flow, and M-mode modalities. 3D echocardiography may add important structural and spatial information in selected cases.

E. Echocardiography methods.

1. Transducer placed directly on the patient's chest (transthoracic echocardiography [TTE]).
2. Transducer mounted on a gastroscope passed into the patient's esophagus and stomach (transesophageal echocardiography [TEE]).

II. INDICATIONS FOR ECHOCARDIOGRAPHY IN THE INTENSIVE CARE UNIT (ICU)

A. Evaluation of left ventricular (LV) and right ventricular structure and function.

1. Estimation of ejection fraction and assessment of parameters such as wall thickness, chamber sizes, regional wall motion abnormalities, and diastolic dysfunction.

†Deceased

2. Doppler echocardiography can provide an accurate assessment of LV filling pressures and stroke volumes.

B. Evaluation of hypotension/shock (Tables 20-1 and 20-2).

C. Evaluation of cardiac valves.

1. Assessment of valvular stenosis or regurgitation requires a comprehensive echocardiographic examination utilizing the 2D, pulsed-wave and continuous-wave Doppler, and color-flow Doppler modalities.
2. Suspected infective endocarditis (IE).
   a. TTE has a sensitivity of 44% to 80% to identify valvular vegetations. TTE is relatively insensitive to diagnose myocardial or aortic root abscesses and infection of prosthetic valves.
   b. TEE has a sensitivity approaching 100% for vegetations as small as 2 mm. TEE can detect complications of IE, such as fistulous tracts, perforation, and abscess formation, in 90% to 95% of cases. It is the modality of choice with suspected prosthetic valve endocarditis or with suspected IE with highly invasive organisms like *Staphylococcus aureus*.

D. Evaluation of the aorta and great vessels.

1. Aortic dissection.
   a. Detection of a mobile intimal flap, aortic regurgitation, pericardial effusion, and aortic rupture.
   b. TEE has higher sensitivity and specificity than TTE and equivalent diagnostic accuracy compared to CT angiography or magnetic resonance imaging.
2. Intramural hematomas and penetrating ulcers and variants of aortic dissection, which can cause acute aortic syndromes.
3. Deceleration injury to aorta/aortic trauma/valvular injuries.

E. Evaluation of hypoxemia.

1. Acute pulmonary embolism: Echocardiography is not a first-line test. It can be helpful for determining RV structure and function for purposes of risk stratification and for emergent evaluation when other testing is not practical.
2. Right-to-left shunting through a patent foramen ovale or via pulmonary arteriovenous malformations (bubble test).
3. Congenital heart lesions.

F. Evaluation of cardiac source of embolism.

G. Evaluation of difficulty to wean from mechanical ventilation.

H. Monitoring of therapeutic procedures (such as pericardiocentesis).

III. ECHOCARDIOGRAPHY PROCEDURE

A. A standard TTE examination is performed by placing an US transducer on the chest and imaging from a variety of areas.

1. In approximately 30% of critically ill patients, the image quality of TTE may be inadequate to obtain necessary diagnostic information. Administration of a microbubble contrast agent may improve the diagnostic utility of bedside TTE in this situation. When image quality

TABLE 20-1 Echocardiographic Features of Various Causes of Hemodynamic Compromise

Diagnosis	LV structure and function	RV size and function	IVC size	Other findings
Distributive shock (e.g., sepsis)	Size most often normal LVEF most often normal to increased About 25%–30% may have reduced LVEF. LV diastolic dysfunction may be present.	Most often normal. Reduced RV systolic function may be observed in a minority of patients.	Often normal or small in size; may be dilated with RV dysfunction	Valvular vegetations and regurgitation may be seen with infective endocarditis.
Cardiogenic shock	Often dilated with reduced LVEF. Focal wall motion abnormalities may be present. Acute processes (such as acute severe AR or MR and VSR) may be associated with normal or increased LVEF and normal LV chamber dimensions.	Dilated, hypokinetic	Dilated	Transient apical ballooning ("Takotsubo") syndrome Aortic or pulmonic stenosis Dynamic LV outflow tract obstruction
Hemorrhagic shock	Small size, hyperdynamic function	Small, hyperkinetic	Small/collapsed	

(Continued)

TABLE 20-1 Echocardiographic Features of Various Causes of Hemodynamic Compromise *(Continued)*

Diagnosis	LV structure and function	RV size and function	IVC size	Other findings
Pulmonary embolism	Normal to small size	Dilated, hypokinetic; increased ratio of RV to LV area	Dilated	Septal flattening and enhanced LV/RV interaction "McConnell sign" Intracavitary thrombus may be observed. Tricuspid regurgitation Right-to-left shunting via PFO
Cardiac tamponade	Small size, hyperdynamic function	Small, diastolic collapse	Dilated	Collapse of the RA and possibly left heart chambers Respiratory variation in mitral and tricuspid E-wave velocities Hemopericardium with myocardial rupture

AR, aortic regurgitation; MR, mitral regurgitation; LV, left ventricle; LVEF, left ventricular ejection fraction; PFO, patent foramen ovale; RA, right atrium; RV, right ventricle; VSR, ventricular septal rupture.

TABLE 20-2 Estimation of Right Atrial Pressure from Assessment of Size and Respiratory Change in Diameter of the Inferior Vena Cava

IVC size[a]	Respiratory change with sniff	RA pressure (mm Hg)
≤ 2.1 cm	Collapse >50%	0–5
≤ 2.1 cm	Collapse <50%	5–10
> 2.1 cm	Collapse >50%	5–10
> 2.1 cm	Collapse <50%	15

[a]Measured at end-expiration just proximal to IVC–hepatic vein junction.
IVC, inferior vena cava; RA, right atrium.

remains an issue or a more detailed evaluation is needed, a TEE will often be required.

2. Limitations of TTE relate primarily to the adequacy of the available acoustic windows: obesity, obstructive lung disease, chest wall injuries, surgical dressings, small rib spaces, inability to move the patient, or previous sternotomy.
3. Contraindications to use of microbubble contrast agents are the presence of right-to-left or bidirectional shunts and known hypersensitivity to perflutren lipid microsphere suspension.
4. TEE requires intubation of the esophagus. Special preparations are required (Table 20-3). TEE is recognized as a superior imaging modality for certain specific indications (Table 20-4).
   a. Limitations of TEE relate to factors such as cooperation, existence of a large hiatus hernia (limit the ability to acquire adequate images), and inability to intubate the esophagus.

TABLE 20-3 Special Preparation for TEE Examination

Nothing per mouth >8 h
Assess for contraindications, insert IV, apply BP cuff, ECG monitor, saturation monitor
Topical anesthesia
Bite block
IV sedation
  Opioid
  Benzodiazepine
  Paralytic (endotracheally intubated patients only)
Code cart available
No requirement for infective endocarditis prophylaxis

IV, intravenous; BP, blood pressure; ECG, electrocardiogram.

TABLE 20-4 Special Indications for TEE

Mitral valve disorders
Cardiac source of embolism/shunts
Cardiac mass lesions
Diseases of the thoracic aorta
Suspected infective endocarditis
Complicated infective endocarditis
Prosthetic valve dysfunction
Poor/inadequate transthoracic images
Guidance of intracardiac therapeutic procedures
Intraoperative monitoring/valve assessment

b. Contraindications to TEE include the presence of significant esophageal pathology (strictures, varices, tumors, Zenker diverticulum, and prior mediastinal irradiation), active upper gastrointestinal (GI) bleeding, recent upper GI surgery, significant coagulopathy, inadequate airway, and lack of patient cooperation.

c. Complications: untoward effects of sedation, hypoxia, bleeding, arrhythmia, angina, methemoglobinemia, esophageal perforation, and death.

IV. POSTPROCEDURE CONSIDERATIONS

A. No special postprocedure considerations are required when a TTE is performed.

B. If a microbubble contrast agent was used, monitor the electrocardiogram (ECG), oxygen saturation, and vital signs for 30 minutes following injection.

C. For TEE, postprocedure considerations include patient recovery from moderate sedation (or general anesthesia in rare instances) and care and cleaning of the probe.

1. Monitoring for a period of no <30 minutes postprocedure is required for all patients receiving moderate sedation. The patient should have nothing by mouth until swallowing, cough, and gag reflexes have returned appropriately.
2. The TEE probe should be wiped down and transported expeditiously to the area where it can be cleaned and reprocessed.
3. The probe should be stored in a protective sheath in an unflexed position.

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Recent guideline publication detailing recommendations for evaluation of the right heart by echocardiography in adults.

21 Arterial Puncture for Blood Gas Analysis

Marie T. Pavini and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Technical considerations

1. Arterial blood gas (ABG) analysis requires a sample of arterial blood for measurement of pH, partial arterial carbon dioxide pressure ($Paco_2$), partial arterial oxygen pressure (Pao_2), bicarbonate (HCO_3^-), and percent oxyhemoglobin saturation (Sao_2) to assess a patient's respiratory, metabolic, and acid–base status.
2. Given the shape of the oxyhemoglobin dissociation curve, oximetry alone for Sao_2 measurement may not be reliable because there must be a substantial fall in Pao_2 before oximetric Sao_2 is appreciably altered. However, the Sao_2 determined by pulse oximetry may be more accurate than calculated Sao_2 from the ABG because the latter value cannot be corrected for variables such as the binding characteristics of hemoglobin (Hb) and 2,3-diphosphoglycerate.
3. The HCO_3^- in an ABG is calculated in contrast to the HCO_3^- measured in venous chemistries.

B. Equipment

1. A glass syringe is the standard to which all other methods are compared. If a large enough needle is used, entry is apparent because the syringe fills by the pressurized arterial flow of blood, without the need for applying a vacuum or using a vacuum-sealed collecting tube.
2. Other plastic ABG kits are available that have directions specific for the type of collection syringe offered (see Section IV.A).

C. Alternative procedures

1. Using correction values, a venous blood gas (VBG) is useful when oxygenation is not suspect (i.e., past ABGs have correlated well enough with oximetric saturations, and there is no suspicion of a substantial change in oxygenation) and the patient is hemodynamically stable.
2. Arterial catheterization is an option if frequent ABG measurements are needed (see Section V.A).

II. INDICATIONS

A. Diagnostic

1. Abnormal acid–base and blood oxygenation can quickly lead to unresponsiveness, serious cardiac arrhythmias, and death and can alert

the physician to reversible causes of tissue hypoperfusion, metabolic derangements, and respiratory arrest.

2. An ABG should be obtained when there is undiagnosed altered mental status, abnormal breathing pattern, suspicion regarding the accuracy of hypoxemia by oximetric saturations, or abnormal HCO_3^- on chemistry laboratory tests.
3. Discrepancy between Sao_2 by pulse oximetry and that calculated by the ABG can aid in the diagnosis of carboxyhemoglobinemia and methemoglobinemia.
4. Values from an ABG allow determination of arterial content of oxygen (Cao_2), oxygen delivery (Do_2), oxygen consumption ($\dot{V}o_2$), and alveolar–arterial Po_2 (A–a) gradient.

III. CONTRAINDICATIONS

A. Puncturing a surgically reconstructed artery may

1. Result in a pseudoaneurysm
2. Compromise the integrity of the graft site
3. Seed the foreign body, rendering it a nidus for infection

B. Severe peripheral vascular disease

1. Diminished or absent peripheral pulses distal to a brachial or femoral puncture
2. Poor collateral circulation

C. Local infection

IV. PROCEDURE

A. Cautions

1. If a plastic syringe is used, the following errors may occur:
   a. Falsely low Pao_2 as O_2 from the sample can diffuse to the atmosphere whenever the sample Po_2 exceeds 221 mm Hg.
   b. Plastic syringes with high surface area to volume ratios (i.e., tuberculin syringes) worsen gas permeability errors compared to 3-mL syringes. For this reason, butterfly infusion kits with their long tubing should not be used.
   c. Plastic syringes tenaciously retain air bubbles and extra effort is required to remove them.
   d. Plastic impedes smooth movement of the plunger, making arterial blood behave like venous blood (i.e., low pressure flow) and raising suspicion that the sample may be venous.
   e. If plunger retraction imparts suction, gas bubbles may be pulled out of solution. If they are expelled, measured Pao_2 and $Paco_2$ tensions may be falsely lowered.
2. Too much heparin causes the concentration of dissolved gases to be closer to that of heparin (Po_2 150 mm Hg; Pco_2 <0.3 mm Hg at sea level and room temperature). There is only a 4% dilution error when 0.2-mL heparin is used for 3- to 5-mL blood, but any less heparin risks a clotted specimen. Crystalline heparin is free of dilutional error but risks clotting.

3. If an ABG specimen is not analyzed within 1 minute of being drawn or not immediately cooled to 2°C, the Pao_2 and pH fall and $Paco_2$ rises due to cellular respiration and consumption of O_2 by leukocytes and platelets. This is of particular concern if leukocytes are >40 × 10^9/L or platelets >1,000 × 10^9/L.
4. Unintentional sampling of the vein will result in a report of a low arterial Po_2.

B. Site selection

1. It is best to select an artery that has good collateral circulation so that if spasm or clotting occurs, the distal tissue is not malperfused. It is also best to select a superficial artery for ease of entry as well as to minimize pain. The radial artery is the preferred site for arterial puncture. The ulnar artery provides sufficient collateral blood flow in approximately 92% of normal adults. The Allen test (or its modification) is not routinely necessary (see Chapter 3) before puncture to determine superficial palmar arch collateral flow.
2. If radial artery sites are not accessible, dorsalis pedis, posterior tibial, superficial temporal (in infants), and brachial and femoral arteries are alternatives (see Chapter 3).
3. Brachial and femoral artery punctures are not advised in patients with coagulopathies because adequate vessel tamponade may not be possible.
4. Any vessel that has been reconstructed surgically should not be punctured (see Section III).

C. Technique

1. Prepare a bag or cup of ice or slush.
2. Perform a time-out.
3. If radial artery is the target, supinate the arm, slightly hyperflex the wrist, and palpate the artery. Secure the patient's hand (i.e., with tape) in this position such that it is rendered immobile.
4. Cleanse the site with a chlorhexidine/alcohol solution or an alcohol swab.
5. You may choose to inject with a 25-gauge needle enough 1% lidocaine intradermally to raise a small wheal where the puncture will be made.
6. Attach a 22-gauge or larger needle to a glass syringe that can accept 5 mL of blood. Wet the needle and syringe with a sodium heparin solution (1,000 units/mL) and express all excess solution or use a regulation ABG kit.
7. With the needle, enter the artery at an angle of approximately 30 degrees to the long axis of the vessel to avoid painful scraping of the periosteum below the artery.
8. As soon as the artery is entered, blood appears in the syringe. Obtain at least 3 mL passively in the glass syringe or the prescribed amount for the commercial ABG kit.
9. Immediately after obtaining the specimen, expel any tiny air bubbles to ensure that the specimen will be anaerobic and that results will be accurate. Remove the needle, cap the syringe, and place in the bag of ice.
10. If using the glass syringe, have an assistant roll it between both palms for 5 to 15 seconds to mix the heparin with the blood.

11. Apply pressure to puncture site for approximately 5 minutes (longer if a coagulopathy is present). If the brachial artery is used, compress the vessel so that the radial pulse cannot be palpated.
12. Immerse the capped sample in a bag of ice and water/slush. (Some kits do not require this step.) Immediately transport the sample to the blood gas analyzer. Many hospitals now utilize point of care testing where blood can be immediately analyzed. Ensure that the sample is labeled with time of draw and ventilator settings (F_{IO_2} if not on ventilator) as well as the temperature of the patient.

V. POSTPROCEDURE CONSIDERATIONS

A. Complications

1. Using the conventional radial artery technique, complications are unusual. These include
   - **a.** Vasovagal episode (rare)
   - **b.** Local pain with or without breath holding (rendering false results)
   - **c.** Limited hematomas (<0.58% of the time) or uncontrolled bleeding
   - **d.** Arterial aneurysm (frequent punctures)
   - **e.** Reflex sympathetic dystrophy (frequent punctures)
   - **f.** Vessel spasm
   - **g.** Needlestick injury to health care personnel
   - **h.** Clotting with possible ischemia and loss of limb
2. Brachial and femoral sites are more difficult to tamponade, making internal bleeding a possibility (especially in coagulopathy).

B. Normal values and corrections

1. pH: 7.35 to 7.45
2. $Paco_2$: 35 to 45 mm Hg
3. Pao_2 (in the normal, nonsmoking, upright person aged 40 to 90): 108.75 (0.39 × age in years) mm Hg
4. Temperature: By convention, ABG specimens are analyzed at 37°C. Although no studies have demonstrated that correction for the patient's temperature is clinically necessary, ABGs drawn at temperatures >39°C should be corrected because the solubility of O_2 and CO_2 increases as blood is cooled rendering hyperthermic patients more acidotic and less hypoxemic than uncorrected values would indicate.
5. When measuring electrolytes from the same arterial collection, a lithium or electrolyte-balanced heparin should be considered as the anticoagulant because sodium heparins may artificially increase sodium levels and lower potassium levels through binding. Dilutional error may still exist if excessive amounts of anticoagulant are used. Point of care testing obviates the need for an anticoagulant as the analysis is performed immediately after collection.

ACKNOWLEDGMENTS

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22 Interventional Ultrasound in the ICU

Gisela I. Banauch and Adam W. Katz

I. ULTRASOUND-GUIDED VASCULAR ACCESS

A. General principles.

1. Avoid injury to adjacent structures through real-time ultrasound (US) imaging/guidance.

B. Indications.

1. Venous cannulation.
- **a.** Internal jugular vein (IJV).
- **b.** Subclavian vein (ScV).
- **c.** Femoral vein.
- **d.** Peripheral veins (piv).

2. Arterial cannulation.
- **a.** Radial artery.
- **b.** Brachial artery.
- **c.** Femoral artery.

C. Procedure.

1. Include both clinical considerations and US imaging in site selection.

2. Identify both vessels of vascular bundle with cross-sectional US prior to needle insertion (exceptions: piv, radial artery). US features suggesting arterial vessel are
- **a.** Pulsation (requires steady US image, possibly absent in hypotension).
- **b.** Less compressibility than accompanying vessel.
- **c.** No respiratory variation.
- **d.** No venous valves.

3. US imaging excludes local contraindications.
- **a.** For venous targets, serial cross-sectional compressions throughout vessel's course proximal to insertion site with fully compressible vein on US indicate absence of thrombi.
- **b.** A vein that collapses with respiration is not accessible to cannulation and often indicates significant intravascular hypovolemia.
- **c.** Arterial aneurysmal dilation contraindicates puncture at that site.

4. US machine position should require only up/down movement to look from sterile field to US screen.
- **a.** IJV: ipsilateral upper chest.
- **b.** ScV: contralateral upper chest.

c. Femoral vessels/radial artery: contralateral lower flank.
d. Brachial artery: contralateral upper chest.
e. Piv: ipsilateral lateral/upper arm.

5. US screen tilt should minimize screen glare.
6. Assure orientation marker is on left side of ultrasound screen.
7. Sterile equipment must include sterile ultrasound transducer cover.
8. Standardize direction of ultrasound transducer marker.
   a. For cross-sectional needle guidance, direct marker to operator's left side. (Ensures that needle movement direction is same on sterile field and on ultrasound screen).
   b. For longitudinal needle guidance, direct marker toward operator. (Ensures that needle insertion occurs on ultrasound screen's left side).
9. Real-time US guidance for vessel puncture.
   a. US imaging plane cross sectional to vessel long axis.
      i. With vessel's cross section in center of ultrasound screen, operator inserts the needle a small distance (e.g., 0.5 cm) as close as possible to ultrasound transducer face long axis' center.
      ii. Sweep transducer cross sectionally along needle long axis and distal to it; then sweep back proximally till needle is again recaptured on US image. The distal/proximal transducer sweep that ends with needle image recaptured assures that needle tip, rather than cross section of more proximal portions of needle shaft, is in scanning plane prior to further advancing the needle.
      iii. Move needle side to side with respect to target vessel's long axis to enhance US visualization of needle.
      iv. Once needle tip is identified on US, assess whether needle direction requires adjustment, then adjust, and insert, similar to Section C.9.a.i. Repeat Sections C.9.a.i to iv till vessel is punctured.
   b. US imaging plane parallel to vessel long axis.
      i. Identify vessel cross sectionally. Prepare sterile needle/syringe.
      ii. Turn transducer to achieve longitudinal vessel image.
      iii. Insert needle while imaging entire extent of needle longitudinally throughout insertion. Pay special attention to maintaining vessel squarely in US image while needle is advanced. It is easy to slide off target vessel onto accompanying vessel without realizing this because US image depicts one vessel only. If this error is not recognized, operator will proceed to puncture the wrong vessel without realizing this.
   c. Longitudinal technique achieves less acute puncture angle—better for deeper vessels.
10. Site-specific considerations.
   a. IJV.
      i. Diameter reduced and vein lies anterior rather than lateral to artery with

(a) Extensive head rotation.
(b) Extensive head extension.
(c) Laryngeal mask airway.

ii. US guidance strongly recommended.

b. ScV.
i. Towel roll between shoulder blades not recommended: decreases cross-sectional area without improving visualization.
ii. Infraclavicular US identification of Sc vein.
(a) With sagittally oriented transducer, scan clavicle medially to laterally till vessels emerge deep to clavicular posterior sound shadow.
(b) Rotate transducer counterclockwise to cross-sectionally image vessels.
(c) Identify vein (see Sections C.2.a. to d.).
(d) Cannulate with longitudinal technique.
iii. US guidance recommended for
(a) Coagulopathy.
(b) Difficult anatomy (including prior failed landmark attempt).

c. Femoral vein.
i. Leg 30 degrees externally rotated.
ii. Puncture close to inguinal ligament—vein lies deep to artery more distally.

d. Radial artery.
i. Avoid wrist extension >60 degrees—overdistends the artery.
ii. US guidance recommended for
(a) Hypotension.
(b) Gross edema.

e. Femoral artery.
i. Leg 30 degrees externally rotated.
ii. US guidance recommended for
(a) Hypotension.
(b) Coagulopathy.
(c) Obesity.

11. Thread guidewire Seldinger fashion into cannulated vessel (except piv).
12. US imaging assures appropriate guidewire placement prior to dilation.
a. Cross-sectional imaging demonstrates vessel compressibility and guidewire position.
b. Longitudinal imaging required to demonstrate that guidewire does not obliquely traverse one vessel and then enter into accompanying (nontargeted) vessel more distally.
13. Seldinger technique for dilation and catheter insertion.
14. US images for documentation.
a. Cross-sectional image with guidewire and vascular compression (see Section C.12.a.).
b. Longitudinal image of guidewire coursing within vessel (see Section C.12.b.).

D. Postprocedure considerations.

1. For vessels close to the chest, reassess whether sliding lung remains present in hemithorax.
2. A chest radiograph is helpful for documenting the position of the tip of the catheter.

II. ULTRASOUND-GUIDED BODY CAVITY ACCESS: PLEURAL, PERITONEAL, AND PERICARDIAL

A. General principles.

1. Avoid injury to adjacent structures through US-facilitated access.

B. Indications.

1. All body cavity punctures; especially
   a. Complex pleural/peritoneal collections.
   b. Morbid obesity, massive edema.

C. Procedure.

1. Refer to US textbooks for identification of fluid collections.
2. Determine site, direction, and depth for needle insertion.
   a. Locate/mark torso site where US image shows maximal extent of fluid collection.
   b. One to two centimeters of fluid in US image throughout all respiratory and cardiac cycles required to assure that deeper organs will not be lacerated.
   c. Meticulously note angle that transducer forms with torso when optimal US image of collection is obtained—this exact angle must be duplicated with needle/syringe assembly.
      i. Real-time guidance usually not needed for pleural/peritoneal puncture, but sterile transducer required for pericardial puncture.
   d. Freeze optimal image and then measure distance from skin to most superficial portion of fluid to determine insertion depth required.
   e. Puncture must follow immediately after site localization.
      i. Ensures optimal duplication with needle/syringe assembly of US transducer angle to torso.
      ii. Minimizes fluid redistribution due to positional change.
3. Procedural pitfalls.
   a. Skin compression.
      i. Falsely short distance from skin to collection due to transducer compressing chest/abdominal wall soft tissues.
      ii. Avoid by applying transducer lightly.
   b. Skin movement.
      i. Suboptimal site marked due to skin being pulled during US identification of insertion site.
      ii. Avoid by applying transducer lightly.
   c. Poor angle duplication.
      i. Suboptimal needle direction due to poor duplication of transducer angle with needle/syringe assembly.
      ii. Strategies to mitigate.

(a) Apply transducer perpendicular to skin (easiest angle to replicate).
(b) Pay meticulous attention to transducer angle during preimaging (see Section C.2.c).

D. Postprocedure considerations.

1. Pleural procedures.
a. If thoracentesis does not yield fluid, verify needle placement ultrasonographically and then consider device insertion/fibrinolysis.
b. Real-time guidance with sterilely sleeved US probe can assist in optimal drainage catheter placement.

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SECTION 2

Palliative Care and Ethical Issues in the ICU

Jennifer Reidy

23 Integrative and Palliative Care in the Intensive Care Unit

Jennifer Reidy, Julia M. Gallagher, and Suzana K. Everett Makowski

I. OVERVIEW

A. General principles: Integrated critical and palliative care improves quality, patient/family satisfaction, and use of ICU resources at end of life.

1. Comprehensive ICU toolkit (www.capc.org/ipal/ipal-icu).
2. Definitions of palliative care and hospice (Table 23-1).

II. PROGNOSTICATION/GOALS OF CARE

A. General principles: Prognostication is crucial for framing medical decisions. Goals-of-care discussions match the values of patients and families with clinical realities and likely treatment outcomes.

1. Tools for assessing pre-ICU prognosis include:
  a. "ePrognosis" (www.eprognosis.org/).
  b. Charlson Comorbidity Index: online calculators available.
  c. Telephone call to primary care physician (PCP) or primary subspecialist.

2. Tools for assessing ICU prognosis.
  a. Acute Physiologic and Chronic Health Evaluation (APACHE IV).
  b. Simplified Acute Physiologic Score (SAPS).
  c. Mortality Prediction Model (MPM).

TABLE 23-1 Comparing Palliative Care and Hospice

	Palliative care	Hospice
Improve quality of life, reduce suffering	Yes	Yes
Bio–psycho–social–spiritual approach	Yes	Yes
Eligibility by prognosis	No (starts from diagnosis of serious illness)	Yes (<6 mo if disease runs its natural course)
Concurrent curative or life-prolonging therapies	Yes	No
Insurance coverage	Varies by insurance	Medicare hospice benefit; most insurances

d. Sequential Organ Failure Assessment (SOFA) score.
e. For diagnosis of brain death, see Chapter 132.

III. STRATEGIES FOR EFFECTIVE COMMUNICATION AND DECISION MAKING

A. General principles: Structured family meetings are the most effective ICU interventions in end-of-life care.
B. Indications: routine meetings in first 2 to 3 days; chronic critical illness; poor prognosis; family and/or staff conflict; major care decision.
C. Procedure: format and steps (see Table 23-2).

1. Pearls.
a. *Listen*: Avoid lecturing; try to sit with strong emotion.
b. *Be patient*: Do not rush to share information before listening; allow people time to process when asking them to make decisions.
c. *Involve family*: Promote consensus and decrease stress/guilt for surrogate decision makers.
d. *Make a recommendation*: After eliciting a patient's values/goals and building relationships, the ICU team should make clear, strong recommendations about care options.

2. When patient lacks capacity to make decisions, use patients' previously stated wishes (advance directives) and substituted judgment.
a. Explain surrogates' role in defining what patients would want if they could speak and understand their situation.
b. If no health care proxy (HCP), state law outlines chain of legal decision makers. If no family, clinicians may use a "best interests" approach; hospitals often seek legal guardianship.

D. Postprocedure: If intractable conflict related to ethical, religious, and cultural values (such as preservation of life at all costs).

1. See "managing conflict"—Table 23-2.
2. Involve consultants in palliative care and ethics.
3. Consider a "harm reduction" approach.

TABLE 23-2 Guide for Effective Family Meetings

Before the meeting

- Review chart; know all medical issues: history, prognosis, and treatment options.
- Coordinate medical opinions among consultant physicians.
- Decide what tests/treatments are likely to benefit the patient.
- Review advance care planning documents.
- Review/obtain family psychosocial information.
- Decide whom you want to be present from family and intradisciplinary team.
- Clarify your goals for the meeting—what decisions are you hoping to achieve?

10-step guide	Helpful language
1) Establish proper setting. Private, comfortable; everyone seated; turn off/forward pager	
2) Introductions. • Allow everyone to state name and relationship to patient. • Ask a nonmedical question.	*"Can you tell me about your father?"* *"What should we know about him that would help us take better care of him?"*
3) Assess understanding. • Ask for a description of changes in function over time.	*"What have the doctors told you about your wife's condition at this point?"*
4) Medical review/summary. • Summarize "big picture" in a few sentences; avoid jargon. • Answer questions.	*"I'm afraid I have some bad news. I wish things were different. Based on what I see, and what you have told me, I believe your mother is dying."*
5) Silence/reactions. • Respond to emotional reactions. • Prepare for common reactions: acceptance, conflict/denial, grief/despair; respond empathically.	*"This must be very hard."* *"I can only imagine how scary/difficult/overwhelming this must be."* *"Can you tell me more about what is upsetting you?"*
6) Discuss prognosis. • Assess how much patient and family want to know. • Provide prognostic data using a range. • Respond to emotion.	*"Some people like to know every detail about their illness; others prefer a more general outline. Which do you prefer?"* *"Although I can't give you an exact time, given your illness and condition, I believe you have* (hours to days) (weeks to months). *This is an average; some live longer and some live shorter."*
7) Assess patient/family goals. • Prolong life. • Improve function. • Return home. • See a family milestone. • Relief of suffering. • Staying in control.	*"What is most important to you at this time?"* *"Are there any important goals or tasks left undone?"* *"Where do you want to be when you die?"*

(continued)

TABLE 23-2 Guide for Effective Family Meetings *(continued)*

8) Present broad care options.
   - Stress priority of comfort, no matter the goal.
   - Make a recommendation based on knowledge/experience.

9) Translate goals into plan.
   - Review current and planned interventions—make recommendations based on goals.
   - Discuss DNR, hospice/home care, artificial nutrition, hospitalizations.
   - Summarize and make follow-up plan.

   Confirm your availability regardless of decisions.

10) Document and discuss.
   - Write a note with follow-up plan.
   - Discuss with team members.
   - Check your emotions.

"Given what you have told me about your mother and her values, I would recommend..."
"If your wife were sitting with us today, what would she say?"

"You have told me her goals are _____. With this in mind, I do not recommend heroic means to prolong your dying process. If you agree, I will write an order that we will not attempt resuscitation when you die. We will continue to do _____ to maximize your comfort, quality of life and meaningful time with family."

Team debriefing = opportunity for teaching and reflection

Ask team members: *"How do you think the meeting went?" "What went well?" "What could have gone more smoothly?" "What will you do differently in the future?"*

Managing conflict

- Listen and make empathic statements.
- Determine source of conflict: guilt, grief, culture, family, trust in team, etc.
- Clarify misconceptions.
- Explore values behind decisions.
- Set time-limited goals with specific benchmarks (i.e., improved cognition, oxygenation, mobility).

When you need assistance or support, consider a palliative care consult.

Adapted from Weissman DE. "The Family Goal Setting Conference" and "Communication Phrases Near the End of Life" pocket cards from Medical College of Wisconsin.

IV. SYMPTOM ASSESSMENT AND TREATMENT

A. General principles: Effective symptom management requires:

1. Avoidance of an "all-or-nothing" approach to comfort.
2. Comprehensive, ongoing assessment and treatment.
3. Intradisciplinary care of the emotional, psychological, social, and spiritual aspects of physical symptoms.
4. Awareness of changing pharmacokinetics in dying patients.
5. Treatment of underlying cause of symptom, if possible (such as thoracentesis of pleural effusions to ease dyspnea).

V. PAIN

A. General principles: See Chapter 105 for assessment, pathophysiology, diagnosis, and treatment. Unique aspects include:

1. Concept of "total pain" (see "Existential and Spiritual Suffering").
2. Avoiding the no-limit, "titrate to comfort" opioid infusion; instead, evaluate prior opioid doses to logically adjust continuous infusions and patient-controlled analgesia.
3. Morphine can cause neurotoxicity (delirium, myoclonus, hyperalgesia, seizures) in patients with renal failure; instead, fentanyl and methadone are drugs of choice.
4. Consider steroids, anticonvulsants, antidepressants, ketamine, intravenous or topical lidocaine, intraspinal analgesics, nerve blocks, cognitive behavioral therapy, complementary medicine, and, as a last resort, palliative sedation.
5. For concise, point-of-care reviews on pain management, see Medical College of Wisconsin's Fast Facts (www.eperc.mcw.edu/EPERC/FastFactsandConcepts).

VI. NONPAIN SYMPTOMS

A. General principles: See Chapters 119, 120 and 142 for etiology, pathophysiology, diagnosis, and treatment of delirium. Unique aspects include:

1. Diagnosing delirium, which is common, multifactorial, and often mistaken for pain. Always seek to prevent and search for reversible causes.
2. Relieving air hunger with opioids and titrating as for pain.
3. Preventing and treating constipation with stimulant laxatives.
4. Evaluating and treating nausea/vomiting based on underlying cause (bowel obstruction, cerebral edema, drug side effect, vestibular symptoms, anxiety, etc.)
5. For concise, point-of-care reviews on many symptoms, see Medical College of Wisconsin's Fast Facts (www.eperc.mcw.edu/EPERC/FastFactsandConcepts).

VII. EXISTENTIAL/SPIRITUAL SUFFERING AND LOSS OF PERSONHOOD

A. General principles: Suffering is multidimensional and unique for each person.

B. Diagnosis.

1. Patient dignity question: *"What do I need to know about you as a person to give you the best care possible?"*(http://dignityincare.ca/en/toolkit.html).
2. HOPE and FICA (validated tools) (www.aafp.org/afp/2001/0101/p81.html).

C. Treatment: Engage pastoral care, social work, and nursing.

1. Preserve patients' sense of self by recognizing their life stories, important relationships, and the impact of illness (http://depts.washington.edu/eolcare/products/communication-tools/).
2. Chaplains are nondenominational and address existential and spiritual suffering, such as loss of meaning/purpose and expressions of guilt.
3. Social workers can address family conflict, financial and placement issues, anticipatory grief, and bereavement care.
4. Nurses palliate symptoms, provide support when patients lose functional capacity, and offer companionship during times of uncertainty and loneliness.

VIII. WITHHOLDING AND WITHDRAWING LIFE-SUSTAINING TREATMENTS

A. General principles: Bioethics and legal precedent support patients' (or their surrogates') choices to withhold or withdraw treatment based on their values.

1. Death occurs as a result of the underlying disease. Any treatment can be withheld or withdrawn, including antibiotics, nutrition, and blood products.

B. Procedure: withdrawal of life support.

1. Most hospitals have established protocols and order sets (http://depts.washington.edu/eolcare/).
2. Steps include:
   - **a.** *Preparation*: Conduct a structured family meeting (Table 23-2); document prognosis, goals of care, and decision-making process; activate all disciplines for support and expertise; create a calm environment; and ask loved ones to gather and allow rituals.
     - **i.** Involve an organ donation professional to explore and discuss organ donation (see Chapters 131 and 132).
     - **ii.** Explain the dying process and acknowledge uncertainty.
   - **b.** Sedation and analgesia: Discontinue paralytics that mask symptoms; write orders (including indications for administration) for IV opioids for pain or air hunger and IV benzodiazepines (anxiety) for treatment before removal of mechanical ventilation and for symptoms that may occur afterward (http://depts.washington.edu/eolcare/).
   - **c.** Removal of life support: Monitor the patient closely for signs of discomfort, and treat symptoms before they become severe. Support the family and allow them meaningful time and physical contact.

IX. TRANSITION OF CARE WHEN PATIENTS SURVIVE TO ICU DISCHARGE

A. Expressions of nonabandonment and clear communication are crucial.

1. Requires ongoing, active engagement of all disciplines with patients and family members.

TABLE 23-3 Discharge to Hospice: Truths and Myths

Truth	Myth
Most insurances pay for intradisciplinary team, medications, equipment, 24/7 hotline.	Hospice provides 24/7 live-in caregivers.
Hospice supports dying patients and their families at their emotional pace.	Patients must "accept" they are dying. Patients must have a "do not resuscitate" order.
Hospice sees patients wherever they live.	Patients must be homebound.
Hospice collaborates with a patient's primary physician.	Patients must give up relationships with primary physicians.
Patients have "comfort packs" of sublingual medications for symptoms as needed.	Hospice hastens death with indiscriminate use of morphine.

2. Continue active medical management while providing comfort-based care, depending on prognosis and goals of care.
3. Document clearly, and speak to receiving clinicians during hand-offs.
4. If discharging patient to hospice, see Tables 23-1 and 23-3.

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SECTION 3

Cardiovascular Problems and Coronary Care

Akshay S. Desai

24 Management of the Resuscitated Post–Cardiac Arrest Patient

Raghu R. Seethala and Benjamin M. Scirica

I. GENERAL PRINCIPLES

A. Despite recent advances in resuscitation care, cardiac arrest remains a leading cause of death worldwide. Even in patients who achieve return of spontaneous circulation (ROSC), mortality rates range between 50% and 75%.

B. Integrated post–cardiac arrest care has become an essential link in the American Heart Association's (AHA's) Chain of Survival.

C. Prolonged whole body ischemia results in the **post–cardiac arrest syndrome (PCAS),** which is defined as a complex multiorgan system process characterized by neurologic injury, myocardial dysfunction, systemic ischemia/reperfusion response, and the precipitating pathology that caused the arrest.

D. The major objectives of post–cardiac arrest care are to institute therapeutic hypothermia (TH) in a timely fashion, identify and treat acute coronary ischemia, ensure adequate end-organ perfusion, maintain appropriate oxygenation and ventilation, and provide general critical care.

II. PATHOPHYSIOLOGY

A. Post–cardiac arrest brain injury.

1. Accounts for a large portion of morbidity and mortality in resuscitated cardiac arrest patients. The brain has limited tolerance to ischemia and has a unique response to reperfusion.
2. Much of the neurologic dysfunction that occurs after ROSC can be attributed to cerebral edema, postischemic neurodegeneration, and impaired cerebrovascular autoregulation.

B. Post–cardiac arrest myocardial dysfunction.

1. Patients can be hemodynamically unstable after ROSC because of a period of global hypokinesis (myocardial stunning) that occurs or directly from the precipitating pathology (e.g. myocardial infarction).
2. Myocardial stunning is usually reversible but can last up to 72 hours.

C. Systemic ischemia/reperfusion response.

1. After ROSC, a sepsis-like state has been described, in which there is a significant systemic inflammatory response syndrome (SIRS) response, impaired vasoregulation, increased coagulation, and adrenal suppression.

D. Persistent precipitating pathology.

1. The underlying cause of the arrest commonly contributes to and complicates the pathophysiologic state of the patient, such as acute coronary syndrome, pulmonary embolism, respiratory failure, electrolyte abnormalities, metabolic abnormalities, environmental insults, toxic exposures, trauma, sepsis, and others.

III. DIAGNOSIS

A. ECG should be performed as soon as possible post-ROSC to determine if an ST-elevation myocardial infarction (STEMI) was the cause of the arrest.

B. Chest x-ray should be performed to detect reversible causes of cardiac arrest (i.e., pneumothorax) and to confirm position of supporting tubes and lines.

C. A head CT should be performed when there is a suspicion that an intracranial event precipitated the cardiac arrest. Otherwise head CT is not mandatory and should not delay further care.

D. CT angiography of the chest if pulmonary embolism or aortic dissection is suspected.

E. Laboratory studies appropriate for critically ill patients should be obtained including complete blood cell count, comprehensive metabolic panel, liver function tests, cardiac enzymes, lactic acid, arterial blood gas, and toxin screen.

IV. TREATMENT (Table 24-1)

A. General measures.

1. Ventilation—A definitive airway (i.e., a cuffed endotracheal tube in the trachea) is required in most cases in patients who are comatose and are hemodynamically unstable. Ensure any temporary airways obtained during arrest are replaced with an advanced airway.

TABLE 24-1 Post-ROSC Treatment

Immediate	First 24 h	After 24 h
Establish definitive airway.	Achieve goal temperature as soon as possible and maintain at 32°C–34°C for 24 h.	Slow and controlled rewarming (0.25°C/h–0.5°C/h).
Obtain IV and arterial access.	Control shivering.	Avoid hyperthermia.
Initiate TH and obtain target temperature <6 h of ROSC.	Continue goal-directed hemodynamic optimization using $ScvO_2$ and lactate clearance as resuscitation end points.	Avoid premature neuroprognostication. Wait at least 72 h until after rewarmed.
Obtain 12-lead ECG, if STEMI initiate reperfusion therapy.	Early echocardiography to assess cardiac function.	
Administer fluid boluses, vasopressors, and inotropes as needed for MAP 65–100 mm Hg.	Consider IABP, VAD, or ECMO in persistently unstable patients.	
Wean FIO_2 as low as possible for goal SaO_2 of 94%–96%.	Glucose control.	
Low tidal volume ventilation (6–8 mL/kg of ideal body weight); goal $PaCO_2$ of 40–45 mm Hg.	Monitor for seizures.	
Specific therapy directed at cause of arrest.		

IV, intravenous; ROSC, return of spontaneous circulation; TH, therapeutic hypothermia; EKG, electrocardiogram; STEMI, ST-elevation myocardial infarction; MAP, mean arterial pressure; FIO_2, fraction of inspired oxygen; $ScvO_2$, central venous oxygen saturation; IABP, intraaortic balloon pump; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation.

2. Access—Most patients post-ROSC will require intensive monitoring including invasive arterial blood pressure monitoring and central venous access for preload optimization and the administration of vasopressors or inotropes.

B. Targeted temperature management.

1. To date, TH is the only therapy post-ROSC that has been shown to improve survival and neurologic outcome. The AHA recommends TH for out-of-hospital cardiac arrest (OHCA) secondary to ventricular tachycardia/ventricular fibrillation (VF/VT) arrests (Class I recommendation) and recommends considering TH in in-hospital cardiac arrest of any rhythm and OHCA of other rhythms.

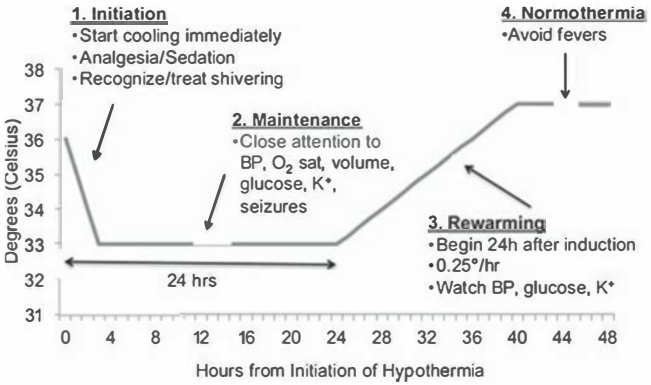

Figure 24-1. Phases of hypothermia. (Reused from Scirica BM. Therapeutic hypothermia after cardiac arrest. *Circulation* 2013;127:244–250, with permission.)

2. Consider TH in patients who are comatose, defined as not having a meaningful response to verbal commands.
3. Cool patients to 32°C to 34°C for 12 to 24 hours. Then slowly rewarm at a rate of 0.25°C/h to 0.5°C/h.
4. Relative contraindications for TH include traumatic arrest, sepsis as the etiology of arrest, coma for other reasons, uncontrolled bleeding, prolonged duration of resuscitation (>60 minutes), or severe intracranial hemorrhage.
5. Phases of TH (Fig. 24-1).
   a. Induction.
      i. Obtain target temperature of 32°C to 34°C as soon as possible with cold saline infusion followed by surface cooling systems or invasive cooling catheters.
      ii. Shivering—common during TH. Control with analgesics, sedatives, and possibly neuromuscular blockade as shivering increases O_2 consumption and significantly decreases cooling rates.
   b. Maintenance.
      i. Usually the most stable phase of TH—avoid major temperature fluctuations.
   c. Rewarming.
      i. Rewarm slowly at a rate of 0.25°C/h to 0.5°C/h to avoid rebound hyperthermia, which can lead to unstable hemodynamics and further neurologic damage.
      ii. Monitor electrolyte as rewarming precipitates hypoglycemia and hyperkalemia.
   d. Normothermia.
      i. Maintain normothermia after TH, as hyperthermia post-ROSC has been shown to be associated with worse outcomes independent of whether patients have undergone TH.

C. Coronary revascularization.

1. Electrocardiogram—Obtain immediately post-ROSC to determine if ST elevations are present, which should prompt immediate consideration for reperfusion, ideally primary percutaneous coronary intervention (PCI).

2. Ischemia without STEMI may also precipitate cardiac arrest, so that even in the absence of STEMI, it may be reasonable to consider angiography.
3. Coronary angiography should not delay TH.

D. Hemodynamics.

1. Hypotension is common secondary to relative volume depletion, vasodilation from the severe SIRS response, and cardiac depression from myocardial stunning or infarct.
2. Early goal-directed therapy.
   a. Initial volume resuscitation to optimize preload.
   b. If still hypotensive, add vasopressors for a goal mean arterial pressure (MAP) between 65 and 100 mm Hg.
3. Echocardiography or invasive hemodynamic monitoring may guide use of inotropes (e.g., dobutamine or milrinone) for hypotension secondary to myocardial depression.
4. Consider mechanical support devices like intraaortic balloon pump, ventricular assist devices, or extracorporeal membrane oxygenation (ECMO) for persistently hemodynamically unstable patients.
5. Goal to achieve $ScvO_2$ >70% and lactate clearance.

E. Oxygenation.

1. Initially during resuscitation, it is common to use 100% oxygen to avoid hypoxia.
2. After ROSC, wean O_2 quickly for a goal SaO_2 of 94% to 96%, as hyperoxia is associated with worse outcomes post-ROSC.

F. Ventilation.

1. Goal $PaCO_2$ of high normal (40 to 45 mm Hg) should be targeted.
2. Avoid hyperventilation with hypocapnia to prevent cerebral vasoconstriction and auto-positive end-expiratory pressure (PEEP).
3. Target a tidal volume of 6 to 8 mL/kg of ideal body weight to prevent lung damage from alveolar over distension.

G. Miscellaneous ICU care.

1. Glucose control.
   a. TH can cause insulin resistance and hyperglycemia. Moderate glycemic control (144 to 200 mg/dL) should be employed.
2. Seizures.
   a. Approximately 5% to 20% of postarrest victims suffer from seizures, which are associated with worse outcomes.
   b. Obtain early and ideally continuous EEG monitoring, as it is common to have nonconvulsive status epilepticus in this setting, in particular, for patients who are paralyzed.

H. Persistent precipitating pathology.

1. Treat the underlying cause of the arrest with case-specific therapy.
2. Fibrinolytic therapy or anticoagulation therapy does not preclude the use of TH.

V. SPECIAL CONSIDERATIONS: NEUROPROGNOSTICATION

A. Neuroprognostication is extremely difficult in the postarrest period. There are no postarrest physical exam findings or diagnostic tests that can accurately predict poor outcome during the first 24 hours.

B. At 72 hours, incomplete recovery of brainstem reflexes, myoclonus, extension posturing or absent motor response to pain, and bilaterally absent somatosensory cortical evoked potentials (N20) were associated with a 0% false-positive rate for poor outcome (American Academy of Neurology Practice Guidelines, 2006). These observations were made in patients who did not undergo TH.

C. TH and the accompanying use of sedative, analgesic, and paralytic medication can delay neurologic recovery. In the setting of TH, traditional prognostic features should be interpreted with caution so as to avoid premature documentation of poor prognosis leading to inappropriate withdrawal of care in patients.

D. Until further investigations are conducted, we recommend attempts to provide neuroprognostication be held at least until 72 hours after patients have been rewarmed.

SUGGESTED READINGS

Delhaye C, Mahmoudi M, Waksman R. Hypothermia therapy: neurological and cardiac benefits. *J Am Coll Cardiol* 2012;59:197–210.
Review that covers role of hypothermia for neurologic and cardiac protection. The role of hypothermia on cardiac protection is not well defined, and this manuscript reviews the existing data.

Kern K. Optimal treatment of patients surviving out-of-hospital cardiac arrest. *JACC Cardiovasc Interv* 2012;5:597–605.
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Kilgannon JH, Jones AE, Shapiro NI, et al. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010;303(21):2165–2171.
A study associating postarrest hyperoxia with increased in-hospital mortality.

Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S768–S786.
Comprehensive guidelines that cover entire post–cardiac arrest care.

Scirica BM. Therapeutic hypothermia after cardiac arrest. *Circulation* 2013;127:244–250.
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Detailed review of therapeutic options.

Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;67:203–210.
A position statement that outlines prognostic indicators after cardiac arrest. Importantly, it does not include data regarding patients who have undergone hypothermia.

25 Management of Hypotension and Cardiogenic Shock

Michael M. Givertz

I. GENERAL PRINCIPLES

A. Background.

1. Hypotension and cardiogenic shock are frequently encountered in the intensive care setting as the final result of a heterogeneous group of disorders.
2. End-organ perfusion generally becomes compromised when the systolic arterial pressure falls below 90 mm Hg or when mean arterial pressure falls below approximately 60 mm Hg. Cardinal manifestations include
   a. Oliguria and worsening renal function.
   b. Metabolic acidosis due to increased production and decreased clearance of lactate.
   c. Mental status changes ranging from confusion to coma.
   d. Cool, clammy skin due to intense vasoconstriction. In patients with distributive shock and low systemic vascular resistance (SVR), extremities may be warm and flushed.
3. Cardiogenic shock is a consequence of severe cardiac pump failure and is characterized by decreased cardiac output, increased SVR, and increased pulmonary capillary wedge pressure. Major causes include:
   a. Massive myocardial infarction; myocardial infarction complicated by ventricular septal, free wall, or papillary muscle rupture; and right ventricular infarction (see Chapter 34).
   b. Advanced nonischemic cardiomyopathy with refractory heart failure.
   c. Fulminant myocarditis or stress cardiomyopathy.
   d. Refractory ventricular tachycardia or severe bradycardia (see Chapters 35 and 38).
   e. Massive pulmonary embolism, pericardial tamponade, or severe pulmonary hypertension.
4. Although definitive management requires therapy directed at the underlying cause of hypotension (e.g., antibiotics for sepsis, corticosteroids for adrenal insufficiency, blood transfusion for bleeding), intravenous (IV) vasoactive agents are at times necessary to maintain perfusion to vital organs while the underlying etiology of hypotension is investigated and definitive measures have been instituted.
5. When IV medications are insufficient to maintain vital organ perfusion, consideration should be given to temporary mechanical circulatory support with an intraaortic balloon pump (IABP), percutaneous

ventricular assist device (VAD), or extracorporeal membrane oxygenation (ECMO).

B. Adrenergic receptor physiology.

1. With few exceptions, vasopressors and positive inotropes are sympathomimetic amines that bind to and stimulate adrenergic receptors. The characteristic hemodynamic effects of individual agents depend to a great extent on selective binding to various adrenergic receptors.
   a. α_1-Adrenergic receptors.
      i. Present in smooth muscle cells of many vascular beds, including the arterioles supplying the skin, mucosa, skeletal muscles, and kidneys, as well as peripheral venules.
      ii. Stimulation causes vasoconstriction and is the most common mechanism of vasopressor action.
      iii. Receptors in the myocardium appear to mediate a modest positive inotropic effect with little change in heart rate (HR).
   b. β_1-Adrenergic receptors.
      i. Predominant adrenergic receptors in the heart.
      ii. Stimulation causes a positive inotropic and chronotropic response.
   c. β_2-Adrenergic receptors.
      i. Stimulation causes relaxation of smooth muscle in the bronchial tree, gastrointestinal tract, and uterus.
      ii. Mediate vasodilation of arterioles supplying skeletal muscle.
   d. Dopaminergic receptors (DA_1 and DA_2).
      i. Mediate renal, coronary, cerebral, and mesenteric vasodilation.
      ii. Stimulate natriuresis.
2. Receptor selectivity of sympathomimetic amines can be drug and/or dose dependent. Examples include:
   a. β_2-receptors are more sensitive to epinephrine than are α_1-receptors.
   b. Dose-dependent actions of dopamine (see Section II.A.3.b).
3. Overall clinical effects of a drug include both the direct sequelae of adrenergic receptor stimulation and the reflex response of homeostatic forces (e.g., norepinephrine-mediated α_1-adrenergic stimulation induces increased vagal tone, which opposes the positive chronotropic effects of β_1-adrenergic stimulation, resulting in little overall change in HR).

II. PHARMACOLOGIC TREATMENT

A. Commonly used vasopressors and positive inotropes (Table 25-1).

1. Epinephrine (Adrenalin).
   a. An endogenous catecholamine, which is the least selective of the vasopressor agents, and a potent agonist of α- and β-adrenergic receptors.
   b. Doses used clinically (1 to 10 μg/min) result in α-mediated venous and arterial constriction and β-mediated increased HR and myocardial contractility. The latter effect is mitigated by increased afterload.
   c. Blood flow to skeletal muscles is increased owing to β_2-mediated vasodilation.
   d. Used to reverse hypotension with or without bradycardia following cardiopulmonary bypass.

TABLE 25-1 Dose Range, Receptor Activity, and Predominant Hemodynamic Effects of IV Vasoactive Drugs Commonly Used to Treat Hypotension

Drug	Dose range	DA	α_1	β_1	β_2	HR	CO	SVR
Dobutamine	2–15 μg/kg/min	–	+	+++	++	↔↑	↑↑	↔↓
Dopamine	1–5 μg/kg/min	+++	–	–	–	↔	↔	↔
	5–10 μg/kg/min	++	+	++	–	↑	↑↑	↔↑
	10–20 μg/kg/min	++	+++	++	–	↑↑	↔↑	↑↑
Epinephrine	1–10 μg/min	–	+++	++	++	↑↑	↑	↑↑
Norepinephrine	0.5–30 μg/min	–	+++	++	–	↔	↔	↑↑
Phenylephrine	40–180 μg/min	–	+++	–	–	↔	↔	↑↑
Ephedrine	10–25 mg q5-10 min	–	++	++	++	↑	↔	↑↑
Vasopressin	0.01–0.05 units/min	–	–	–	–	↔	↔↓	↑↑

HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance.

e. Plays a central role in cardiovascular resuscitation and management of anaphylaxis (see Chapter 140).

f. Because of adverse effects on renal and splanchnic blood flow and potential for inducing myocardial ischemia and tachyarrhythmias, epinephrine is considered a second-line agent in the management of hypotension secondary to septic shock.

g. May cause restlessness, tremor, headache, and palpitations.

2. Norepinephrine (Levophed).

a. An endogenous catecholamine with potent α_1- and β_1-adrenergic activity but little β_2-agonism.

b. Predominant effect is dose-dependent vasoconstriction of arterial resistance vessels and veins. Cardiac effects of β_1-stimulation are counterbalanced by increased afterload and reflex vagal activity induced by elevated SVR.

c. Clinically used doses (0.5 to 30 μg/min) result in potent vasoconstriction. Generally infused as a second-line agent in cases of severe distributive shock, but several studies suggest that in adults with hyperdynamic septic shock, use of norepinephrine as the initial agent is more likely to result in improved blood pressure and survival compared to dopamine.

d. Adverse effects include increased myocardial oxygen consumption and excessive renal and mesenteric vasoconstriction. Renal ischemia may be of particular concern in patients with hemorrhagic shock.

e. Extravasation often causes tissue necrosis and may lead to skin sloughing, and should be managed with local infiltration of phentolamine (see Section III.F).

3. Dopamine (Intropin).

a. An endogenous catecholamine that functions as a central neurotransmitter and synthetic precursor to norepinephrine.

b. Stimulates dopaminergic and adrenergic receptors in a dose-dependent manner; also stimulates release of norepinephrine from nerve terminals.
  i. Low dose (<5 μg/kg/min): predominantly stimulates dopaminergic receptors in renal, mesenteric, and coronary vessels. In normal subjects, low-dose dopamine augments renal blood flow with little effect on blood pressure. The strategy of using low-dose dopamine as a renoprotective agent in critically ill patients has not been shown to be effective in controlled studies.
  ii. Moderate dose (5 to 10 μg/kg/min): Predominant effect is β_1-mediated augmentation of myocardial contractility and HR.
  iii. High dose (>10 μg/kg/min): Overall hemodynamic effect resembles that of norepinephrine and is mediated by α_1-adrenergic receptor stimulation.

c. As an agent with both inotropic and vasopressor activity, moderate- to high-dose dopamine has the versatility to be used as a first-line agent in hypotension of unknown etiology. However, in the setting of severe hypotension due to septic shock, a more potent α-adrenergic agonist such as norepinephrine may be more effective in restoring perfusion pressure.

d. By itself or in combination with other positive inotropes such as dobutamine, moderate-dose dopamine may be used in the management of hypotensive patients with acute decompensated heart failure.

e. Adverse effects include dose-dependent tachycardia, tachyarrhythmias, and excessive vasoconstriction, which in patients with coronary artery disease can result in ischemia due to increased myocardial oxygen consumption coupled with some degree of coronary vasoconstriction.

f. Use in septic shock may cause splanchnic shunting, impaired gastric mucosal oxygenation, and increased risk of gastrointestinal bleeding.

4. Dobutamine (Dobutrex).

a. A synthetic sympathomimetic amine that causes potent nonselective β- and mild α-adrenergic stimulation. Its mechanism of action is complex and involves two stereoisomers with distinct affinities for different adrenergic receptors (see main text).

b. Doses used clinically (2 to 15 μg/kg/min or higher) increase cardiac contractility and HR. The positive chronotropic effect occurs to a lesser extent than with dopamine. SVR is modestly reduced or may remain unchanged.

c. Useful for temporary inotropic support of hypotensive patients with acute decompensated heart failure and patients with concomitant septic shock and depressed cardiac function and a mixed venous oxygen saturation less than 70%.

d. In patients with marked hypotension, the initial effect on blood pressure may be unpredictable. In this setting, dobutamine should be administered in combination with a vasopressor such as dopamine or norepinephrine.

e. As with other positive inotropic agents, increased myocardial oxygen consumption may worsen cardiac ischemia, and tachycardia or arrhythmias may limit dose titration. In patients with acute decompensated heart failure, inotropic response may be variable, and short-term or intermittent dobutamine therapy has been associated with excess mortality.

f. Chronic therapy may cause an eosinophilic or hypersensitivity myocarditis resulting in hemodynamic deterioration.

5. Phenylephrine (Neo-Synephrine).

a. A synthetic sympathomimetic amine that selectively stimulates α_1-adrenergic receptors, causing dose-dependent arterial vasoconstriction. Increased blood pressure can activate vagal reflexes, causing slowing of the HR.

b. Although there are little data regarding its relative efficacy compared to older vasopressors, phenylephrine is frequently infused at 40 to 180 μg/min to treat vasodilatory or hyperdynamic septic shock. It is also commonly used to treat anesthesia-induced hypotension.

c. The absence of β-agonist activity at usual doses has made phenylephrine an attractive agent in clinical situations where tachycardia or tachyarrhythmias limit the use of other agents.

d. High-dose phenylephrine can cause excess vasoconstriction, and patients with left ventricular systolic dysfunction may not tolerate the α_1-mediated increase in afterload.

e. Compared to epinephrine and norepinephrine, phenylephrine is less likely to decrease microcirculatory blood flow in the gastrointestinal tract.

6. Ephedrine.

a. A naturally occurring sympathomimetic amine derived from plants that nonselectively activates adrenergic receptors and stimulates norepinephrine release from storage sites.

b. Similar hemodynamic profile (e.g., cardiac stimulation and peripheral vasoconstriction) and adverse effects (e.g., myocardial ischemia and excessive vasoconstriction) as epinephrine.

c. Rarely used in the critical care setting except in the temporary treatment of hypotension induced by spinal anesthesia.

7. Vasopressin (Pitressin).

a. An endogenous antidiuretic hormone that has emerged as a potential alternative to adrenergic vasopressors for treatment of refractory vasodilatory shock. The mechanism of pressor action has not been fully elucidated, but involves binding to V_{1A} receptors on vascular smooth muscle.

b. Minimal effect on blood pressure in healthy subjects, but increases blood pressure in patients with septic shock or vasodilatory shock following cardiopulmonary bypass and has been shown to facilitate the tapering of adrenergic agents in these settings.

c. It remains unclear whether hemodynamic benefits are confined to a subset of patients with relative vasopressin deficiency, hypersensitivity, or both.

d. Currently recommended in doses of 0.01 to 0.05 units/min as an adjunctive agent in the treatment of vasodilatory septic shock that is poorly responsive to traditional adrenergic agonists. Also, may be given as a one-time dose of 40 units IV to replace first or second dose of epinephrine in cardiac arrest due to pulseless electrical activity. Use as a stand-alone vasopressor has not been well studied.

e. Potential adverse effects include excess vasoconstriction causing end-organ hypoperfusion including myocardial ischemia. Cardiac output (CO) may also worsen due to excessive afterload.

f. Terlipressin is a synthetic long-acting analogue of vasopressin that is currently being tested in patients with septic shock and hepatorenal syndrome.

B. Adjunctive agents.

1. Methylene blue (Urolene Blue).
- **a.** Inhibits guanylate cyclase, the target enzyme of endothelium-derived nitric oxide (NO).
- **b.** Administered as a one-time IV bolus in a dose of 1 to 2 mg/kg to treat refractory hypotension (or vasoplegia syndrome) following cardiopulmonary bypass or cardiac transplantation.
- **c.** Potential adverse effects include hypertension, cardiac dysrhythmias, malignant hyperthermia, and hemolytic anemia.

2. Hormones.
- **a.** Several hormones including cortisol and thyroxine play important roles in the maintenance of vascular tone, and their absolute or relative deficiency may contribute to hypotension in the critically ill patient (see Chapters 84 and 85).

3. Calcium.
- **a.** Indications for acute administration in the hypotensive patient include correction of clinically significant hyperkalemia or hypocalcemia and as an antidote to calcium channel blocker or beta-blocker overdose.
- **b.** Calcium chloride (100 mg/mL) is usually given as a slow IV push of 5 to 10 mL and may be repeated as needed. Ionized calcium should be followed.

C. Choosing an agent (Table 25-2).

1. There are no large adequately controlled trials to guide the pharmacologic management of hypotension. Consensus recommendations are based on animal studies and small clinical trials. The selection of an appropriate agent should be made on a case-by-case basis, with attention to the known or suspected underlying cause.

2. Given its combined pressor and positive inotropic properties, moderate- to high-dose dopamine is a reasonable choice for the initial treatment of hypotension of unknown etiology. For the treatment of severe hypotension (systolic blood pressure <70 mm Hg), a more potent α_1-adrenergic agonist such as norepinephrine should be considered.

3. Norepinephrine may be the pressor of choice in the treatment of vasodilatory shock related to sepsis. In cases where tachycardia, tachyarrhythmias, or both limit dose titration of other agents, phenylephrine is a useful alternative. Epinephrine can be added for refractory septic shock.

4. For the mildly hypotensive patient with left ventricular systolic dysfunction, dobutamine is the drug of choice. With frank cardiogenic shock or combined vasodilation and pump failure, dopamine can be used as a single agent or in combination with other drugs such as dobutamine.

5. In patients with septic shock and associated myocardial dysfunction, dobutamine can be added to norepinephrine for added positive inotropic support.

TABLE 25-2 Hemodynamic Profiles of Selected Causes of Hypotension and Commonly Used First-Line Agents

Cause of hypotension	PCWP	CO	SVR	Preferred agent(s)
Unknown	?	?	?	Dopamine
Hypovolemia	↓	↓	↑	None[a]
Acute decompensated heart failure	↑	↓	↑	Dopamine, Dobutamine
Cardiogenic shock	↑↔	↓	↑	Dopamine
Hyperdynamic sepsis	↓↔	↑	↓	Norepinephrine, Dopamine
Sepsis with LV dysfunction	?	↓	↓	Dopamine, Norepinephrine plus dobutamine
Anaphylaxis	?	?	↓	Epinephrine
Anesthesia-induced hypotension	?	?	↓	Phenylephrine, Ephedrine[b]

↓, decrease; ↑, increase; ↔, no change; ?, unknown.
[a]Volume resuscitation with intravenous fluids and/or blood products recommended.
[b]For obstetric patients.
PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance; LV, left ventricle.

6. Vasopressin is a useful adjunctive agent for treatment of the septic patient with hemodynamic collapse resistant to adequate fluid resuscitation and high-dose conventional vasopressors.
7. For patients refractory to multiple pressors, including those status post-cardiopulmonary bypass, a trial of methylene blue should be considered.

III. HEMODYNAMIC MONITORING AND COMPLICATIONS

A. Vasopressors and positive inotropes are potent agents with considerable potential for toxicity mediated by the same mechanisms that increase blood pressure. They should be used with extreme caution and at the lowest dose required to maintain end-organ perfusion.

1. Tachycardia and tachyarrhythmias result from β_1-stimulation and can limit the use of these agents in patients with underlying cardiovascular disease.
2. Depressed left ventricular systolic function may develop as a result of increased afterload or secondary to ischemia.
3. Myocardial ischemia may be caused by coronary vasoconstriction or more commonly by increased myocardial oxygen demand.
4. Excessive arterial vasoconstriction can compromise splanchnic and renal perfusion. Similarly, peripheral limb ischemia and digital necrosis may occur.

B. Monitoring.

1. Patients should be treated in an intensive care setting with continuous monitoring of cardiac rhythm, urine output, and arterial oxygenation.

2. Intra-arterial cannulation and direct monitoring of blood pressure are suggested during prolonged vasopressor use.
3. Fluid resuscitation and careful attention to intravascular volume are paramount as many patients with hypotension can be stabilized with fluids alone, and the administration of vasopressors to hypovolemic patients can worsen end-organ perfusion. The use of central venous or pulmonary artery catheters to monitor filling pressures can be helpful in selected cases, but the routine use of invasive hemodynamic monitoring is not necessary and may be harmful.
4. Minimally invasive hemodynamic monitors (e.g., Vigileo, PiCCO, PhysioFlow) have emerged as an alternative to pulmonary artery catheters to manage critically ill patients in the intensive care unit.
   a. These devices measure cardiac output by one of four main principles: pulse contour analysis, pulsed Doppler technology, applied Fick principle, and bioimpedance (or bioreactance).
   b. In addition to stroke volume and CO, may provide static preload variables (e.g., global end-diastolic volume), functional hemodynamic variables (e.g., stroke volume variation), and continuous central venous oxygen saturation ($ScvO_2$).
   c. No single device has been shown to improve patient outcomes.
5. Although a mean arterial pressure of >60 mm Hg is usually required to maintain autoregulatory blood flow to vital organs, some patients may require higher or lower pressures. It is essential to monitor carefully other indicators of global and regional perfusion such as mental status and urine output. Following mixed venous oxygen saturation and serum lactate levels, and monitoring intramucosal pH by gastric tonometry may be useful but are not advocated for routine use.

C. With few exceptions, these drugs are short-acting agents with rapid onset and offset of action. They are generally initiated without a bolus and can be titrated frequently. Abrupt lowering and discontinuation of vasoactive drugs should be avoided to prevent rebound hypotension. Vasopressin, in particular, requires very slow weaning as low doses are achieved.

D. There is considerable variation in the initial dose required to restore adequate hemodynamics. Moreover, an individual patient's responsiveness to a given agent may diminish over time owing to several mechanisms including adrenergic receptor desensitization.

E. Careful attention should be paid to potential drug–drug interactions.

1. Recent or current treatment with β-adrenergic antagonists can cause resistance to the action of dobutamine and other β-receptor agonists.
2. The administration of less selective adrenergic agonists such as epinephrine to patients treated with β-blockers can cause unopposed α-adrenergic stimulation.
3. Patients taking monoamine oxidase inhibitors may experience an exaggerated response to some catecholamines and should be treated with a very low (<10%) starting dose.

F. Drugs should generally be administered through central venous catheters using volumetric infusion pumps that deliver precise flow rates. In the event

of vasopressor extravasation, an α_1-adrenergic antagonist (e.g., phentolamine 5 to 10 mg diluted in 10 to 15 mL of saline) can be infiltrated into the area to limit local vasoconstriction and tissue necrosis.

IV. MECHANICAL CIRCULATORY SUPPORT

A. Background.

1. For patients with cardiogenic shock who do not respond to positive inotropic or vasopressor agents, urgent consideration should be given to support with an IABP or percutaneous VAD. ECMO should reserved for specialized centers and clinical circumstances.
2. The most common setting in which an IABP is used for temporary support is acute myocardial infarction complicated by cardiogenic shock.
3. In patients with end-stage heart failure, worsening hemodynamics and end-organ dysfunction, IABP or percutaneous VADs can also be used as a bridge to surgical VAD (so-called bridge to bridge) or cardiac transplantation.
   a. Restoration of normal cardiac output allows time for further assessment of end-organ function, including renal, hepatic, and pulmonary function, as well as for neurologic recovery.
   b. Given the increase in waiting list times in many regions, IABP or percutaneous VAD is not a feasible method of providing prolonged support (i.e., weeks to months) and precludes pretransplant rehabilitation.
4. Decisions regarding the use of mechanical circulatory support.
   a. Should be made in consultation with an advanced heart disease specialist, an interventional cardiologist, and a VAD/transplant surgeon.
   b. Require evaluation and management by a multidisciplinary team.

B. Intra-aortic balloon counterpulsation.

1. In the setting of cardiogenic shock complicating acute myocardial infarction, IABP is commonly used to reduce ischemia (by improving diastolic coronary blood flow) and improve hemodynamics (by reducing myocardial afterload) while awaiting more definitive treatment (e.g., percutaneous or surgical revascularization or repair of a mechanical complication such as a papillary muscle rupture or ventricular septal defect).
   a. In US and European guidelines, the use of IABP in the treatment of cardiogenic shock is given a class IB and class IC recommendation, respectively. Evidence is based mainly on registry data.
   b. The IABP SHOCK II Trial (see Suggested Readings) randomized 600 patients with cardiogenic shock complicating acute myocardial infarction who were expected to undergo early revascularization to IABP or no IABP.
      i. The use of IABP did not reduce 30-day mortality.
      ii. There were no differences in time to hemodynamic stabilization, length of ICU stay, dose and duration of catecholamine therapy, and renal function.
      iii. The groups did not differ significantly with respect to rates of major bleeding, peripheral ischemic complications, sepsis, and stroke.

2. Balloon counterpulsation may support a patient while waiting for spontaneous recovery of stunned myocardium due to ischemia, acute myocarditis, or stress cardiomyopathy.
3. Absolute contraindications to IABP include aortic insufficiency, aortic dissection, and significant peripheral arterial disease involving the abdominal aorta or iliofemoral arteries.
4. Relative contraindications include gastrointestinal bleeding, thrombocytopenia, abdominal aortic aneurysm, or presence of a vascular graft.
5. The overall complication rate of IABP use is approximately 5%.
   a. Complications during insertion include failure of IABP to pass the iliofemoral system due to atherosclerotic occlusive disease (5% to 7%) and aortic dissection or arterial perforation (1% to 2%).
   b. Complications during counterpulsation include limb ischemia that is sufficiently severe to require device removal (6%); infection, thrombocytopenia, and embolization of platelet aggregates or atherosclerotic debris; and rupture of the balloon (2%) that may cause gas embolization.
   c. Complications during/after removal include impaired arterial perfusion of the limb, puncture site–related hematoma, pseudoaneurysm, or arteriovenous fistula.

C. Percutaneous ventricular assist device.

1. Indications.
   a. Current ACCF/AHA/SCAI guidelines discuss use of percutaneous VADs as an adjunct to high-risk percutaneous coronary intervention and for cardiogenic shock or ventricular septal rupture complicating acute myocardial infarction.
   b. Increasingly, percutaneous VADs are used for stabilizing critically ill patients with end-stage heart failure and cardiogenic shock while awaiting a decision regarding candidacy for heart transplant or destination VAD therapy.
   c. Selected patients with reversible forms of severe, acute myocardial failure (e.g., peripartum or stress cardiomyopathy) may bridge to recovery on percutaneous VADs.
   d. Emerging/novel indications for percutaneous VAD support include:
      i. High-risk patients undergoing percutaneous valve repair/replacement or ventricular tachycardia mapping and ablation.
      ii. Patients requiring temporary right ventricular support in the setting of massive pulmonary embolism or following surgical left ventricular assist device (LVAD) placement or heart transplant.
2. Potential hemodynamic benefits of percutaneous VADs include:
   a. Maintaining vital organ perfusion.
   b. Reducing right and left heart filling pressures.
   c. Reducing left ventricular wall stress and myocardial oxygen consumption.
   d. Increasing coronary artery perfusion pressure.
3. There are two major types of continuous flow percutaneous ventricular assist devices available for clinical use:
   a. The TandemHeart pVAD (CardiacAssist, Inc.) withdraws blood from the left atrium (using a transseptal cannula) and ejects blood into the femoral artery.

b. The Impella 2.5 and 5.0 systems (ABIOMED) withdraw blood from the left ventricle (using a catheter placed retrograde across the aortic valve) and eject blood into the ascending aorta.

4. General contraindications to percutaneous VAD use include bleeding diatheses and severe peripheral arterial disease. Other contraindications are device specific.

a. TandemHeart: moderate–severe aortic stenosis and regurgitation, presence of an atrial septal defect or previously placed occluder device.

b. Impella 2.5 and 5.0: mechanical aortic valve, moderate or severe aortic insufficiency, left ventricular thrombus.

5. Percutaneous VADs can generate up to 5 L of blood flow per minute and rapidly reverse end-organ dysfunction associated with severe, refractory cardiogenic shock.

6. Open-label studies comparing percutaneous VADs with balloon counterpulsation demonstrate superior hemodynamic benefit but fail to show any difference in short-term morbidity or mortality (30-day mortality approximately 40%).

7. Major risks include bleeding, TIA/stroke, infection, and vascular complications. Hemolysis may occur due to improper device positioning.

8. The role of partial percutaneous VAD support (e.g., Impella 2.5) in the setting of high-risk percutaneous revascularization remains unproven.

D. Extracorporeal membrane oxygenation.

1. For patients with severe cardiac and/or respiratory failure, ECMO can provide support for up to 1 week or longer.

2. Indications include severe shock in the setting of acute myocardial infarction, fulminant myocarditis, massive pulmonary embolism, or cardiac arrest or failure to wean from cardiopulmonary bypass. ECMO may also be used to support patients with severe allograft dysfunction following heart transplant and with high-frequency ventilation to treat severe acute respiratory distress syndrome.

3. Blood is withdrawn from the circulation via an inflow cannula into an extracorporeal continuous flow pump, passed through an oxygenator, and then returned to the patient through an outflow cannula. There are two types of ECMO.

a. Venovenous (VV): Deoxygenated blood is withdrawn from a large central or peripheral vein (internal jugular or femoral), and oxygenated blood is returned to another large vein. Provides pulmonary support only.

b. Venoarterial (VA): Typically, deoxygenated blood is withdrawn from a femoral vein, and oxygenated blood is returned to a femoral artery. Provides full cardiac and pulmonary support.

4. Anticoagulation, typically with unfractionated heparin, is targeted to an ACT of 180 to 250 seconds.

a. ECMO is contraindicated in patients with active gastrointestinal bleeding or recent stroke.

5. Major complications include bleeding (30% to 40%), thromboembolism (greater with VA ECMO), cannulation-related vessel injury or ischemia, and heparin-induced thrombocytopenia.
6. Neurologic injury, including coma, encephalopathy, anoxic brain injury, stroke, and brain death, has been reported in up to 50% of patients who received ECMO for more than 12 hours. This high incidence may be due to the severity of the underlying illness and the indication for ECMO support rather than a direct complication of the device.
7. ECMO is a resource-intensive treatment modality that should be reserved for major centers with a dedicated, highly trained, and multidisciplinary staff.

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26 The Cardiomyopathies: Diagnosis and ICU Management

G. William Dec

I. BACKGROUND

A. Cardiomyopathies are a diverse group of diseases characterized by primary myocardial involvement.

B. Classified by anatomic appearance and physiologic abnormalities (Table 26-1).

1. Dilated cardiomyopathies (DCMs).

2. Hypertrophic cardiomyopathies (HCMs).

3. Restrictive cardiomyopathies (RCMs).

II. DILATED CARDIOMYOPATHIES

A. Background.

1. Cardiac enlargement (left ventricular [LV] end-diastolic dimension >55 mm) and decreased contractile function (left ventricular ejection fraction [LVEF] < 45%) are disease hallmarks.

2. Reversible causes should always be excluded (Table 26-2).

3. A familial pattern is present in approximately 25% of cases; clinical clues are the following:

a. Concomitant skeletal myopathy, often mild.

b. Sensorineural hearing loss.

B. Pathophysiology.

1. Impaired systolic contractile function leads to ventricular dilatation via the Frank-Starling mechanism.

2. Functional mitral and/or tricuspid regurgitation is common as annular displacement occurs secondary to progressive ventricular dilatation.

3. Chronic dyspnea due to elevated filling pressures is the most frequent symptom. Acute pulmonary edema is uncommon except during periods of stress (e.g., infection, change in cardiac rhythm, surgical procedures).

4. Physical findings.

a. Jugular venous distension and hepatojugular reflux.

b. S4 and S3 gallops may wax and wane in intensity.

c. Mitral or tricuspid regurgitation murmurs (1–3/6 in intensity) are often audible.

d. Clear lungs are most commonly due to enhanced pulmonary lymphatic drainage.

e. Liver enlargement and peripheral edema are seen in fewer than 50% of cases.

TABLE 26-1 Hemodynamic and Morphometric Features of the Cardiomyopathies

Features	Dilated	Hypertrophic	Restrictive
LV ejection fraction	<45%	65%–90%	50%–70% <40% (late)
LV cavity size	Increased	Normal or decreased	Normal Increased (late)
Stroke volume	Markedly decreased	Normal or increased	Normal or decreased
Volume to mass ratio	Increased	Decreased	Markedly decreased
Diastolic compliance	Normal to decreased	Markedly decreased	Markedly decreased
Other features	Mild/moderate MR/TR are common	Dynamic obstruction	Often mimics constrictive pericarditis

DCM: dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; TR, tricuspid regurgitation.
Adapted from DeSanctis RW, Dec GW. The cardiomyopathies. Section 1, Subsection XIV, in Scientific American Medicine, Dale DC and Federman D (eds). Copyright 1995, Scientific American, Inc. (Table 1), with permission.

C. Diagnosis.

1. Echocardiography is the most useful noninvasive modality to assess systolic and diastolic function, chamber size, and ventricular wall thickness and to exclude significant valvular pathology (Table 26-3).
2. Patients with known DCM and stable symptoms require little additional diagnostic testing.
   a. Serum electrolytes, Mg^{2+}, and B-type natriuretic peptide (BNP) may help direct treatment and risk stratification.
   b. 12-lead ECG and CXR.
   c. Preoperative echocardiography is generally unnecessary in patients who have been clinically stable at home and are ambulatory.
   d. Preoperative pharmacologic stress testing with cardiac perfusion imaging should be considered for patients with known or suspected ischemic cardiomyopathy and either worsening heart failure or anginal symptoms or in whom a major surgical procedure is planned.

D. Treatment.

1. Elective surgery should be postponed for patients with newly diagnosed DCM to initiate pharmacologic therapy and allow time (6 to 12 weeks) for spontaneous recovery of systolic function.
2. Heart failure decompensation is the most frequent complication during ICU hospitalization.
3. Individuals whose LVEF <20% are at increased risk for developing perioperative heart failure, atrial fibrillation, ventricular arrhythmias, and cardiorenal syndrome.

TABLE 26-2 Causes of Potentially Reversible DCM

Toxins

Ethanol
Cocaine
Antiretroviral agents (AZT, ddI, ddC)
Phenothiazines, clozapine
Chemotherapeutic agents (anthracyclines, trastuzumab)

Metabolic abnormalities

Nutritional (thiamine, selenium, carnitine, and taurine deficiencies)
Endocrinologic (hypothyroidism, acromegaly, thyrotoxicosis, pheochromocytoma)
Electrolyte disturbances (hypocalcemia, hypophosphatemia)

Inflammatory/infectious/infiltrative

Infectious
- Viral (coxsackievirus, adenovirus, cytomegalovirus, parvovirus)
- Parasitic (toxoplasmosis)
- Spirochetal (Lyme disease)

Inflammatory/Infiltrative
- Collagen vascular disorders (sarcoidosis)
- Hypersensitivity myocarditis
- Hemochromatosis
- Sarcoidosis

Miscellaneous

Tachycardia induced
Idiopathic
Peripartum

AZT, zidovudine (azidothymidine); ddI, didanosine (dideoxyinosine); ddC, zalcitabine (dideoxycytidine).

4. The cornerstones of pharmacologic therapy should include:
   a. A loop diuretic (furosemide, bumetanide, or torsemide).
   b. An ACE inhibitor or angiotensin receptor blocker (ARB).
   c. A β-blocker.
   d. Digoxin and aldosterone antagonists are generally reserved for patients with chronic advanced (New York Heart Association [NYHA] class III or IV) symptoms.
5. Acute volume expansion should be avoided as it will exacerbate atrioventricular (AV) valvular regurgitation and lead to decreased forward stroke volume and cardiac index.
6. Hemodynamic monitoring with a pulmonary artery catheter should be considered for major surgical procedures in DCM patients who have
   a. Recent decompensation in heart failure symptoms.
   b. Myocardial infarction within the previous 3 months.
   c. Moderate/severe stenotic valvular heart disease.

TABLE 26-3 Diagnostic Evaluation of New-Onset DCM

Class I studies (*usually indicated, always acceptable*)
CBC and urinalysis
Electrolytes, renal function, glucose, phosphorus, calcium, albumin, TSH level
Chest film, electrocardiogram
Transthoracic Doppler echocardiogram
Noninvasive stress testing (or coronary CT angiography) in patients who lack angina but who have a high probability of underlying ischemic heart disease, a known prior myocardial infarction, or extensive areas of hibernating myocardium (*Note:* Patients should be suitable candidates for revascularization if extensive ischemia is detected.)

Class II studies (*acceptable but of uncertain efficacy; controversial*)
Serum iron/ferritin
Noninvasive stress testing in all patients with unexplained DCM
Coronary angiography in all patients with unexplained DCM
Endomyocardial biopsy in patients with:
Cardiomyopathy of recent onset (generally <6 mo) and rapid deterioration in ventricular function
Clinically suspected granulomatous myocarditis
Cardiomyopathy and a systemic disease known to involve the myocardium (e.g., sarcoidosis, hemochromatosis)

Class III studies (*generally not indicated*)
Routine 24-h ambulatory ECG monitoring
Serial echocardiography in clinically stable patients
Routine right heart catheterization to guide medical therapy
Endomyocardial biopsy in chronic DCM
Cardiac catheterization in patients who are not candidates for revascularization, valve replacement, or cardiac transplantation

CBC, complete blood count; TSH, thyroid-stimulating hormone; ECG, electrocardiogram.
Adapted from American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2009 Focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults. *Circulation* 2009;119:1977–2016.

7. Hemodynamic goals for DCM management in ICU setting.
   a. PCW 15 to 18 mm Hg.
   b. CI > 2.2 L/min/m^2.
8. For hemodynamically unstable patients, oral vasodilators should be replaced with short-acting intravenous agents (e.g., nitroprusside, nitroglycerin, or nesiritide). Occasionally, a beta-agonist (dobutamine) or a phosphodiesterase III inhibitor (milrinone) may be required for acute management of a low-output state.
9. Rapid atrial fibrillation is not uncommon during hospitalization due to enhanced sympathetic tone. Acceptable agents to control heart rate may include beta-blockers, digoxin, and intravenous amiodarone.

10. Asymptomatic, nonsustained ventricular arrhythmias generally do not require pharmacologic suppression. Intravenous amiodarone and Xylocaine are the agents of choice for symptomatic ventricular tachyarrhythmias.

E. Prognosis.

1. Prognosis is highly dependent upon disease etiology.
   a. Idiopathic DCM: 5-year survival rate = 80%.
   b. HIV and chemotherapy-related cardiomyopathies: 5-year survival rate <25%.
2. Spontaneous improvement occurs in 20% to 40% of cases if symptom duration is short (<6 months).
3. Clinical, echocardiographic, and laboratory findings are useful for identifying high-risk patients (Table 26-4).

TABLE 26-4 High-Risk Features in DCM

Clinical features

NYHA class IV symptoms on admission
Recent onset of illness (<6 mo)
Active myocardial ischemia (angina or ischemic ECG abnormalities)
History of syncope
Persistent S_3 gallop
Right-sided heart failure signs
Inability to tolerate ACE inhibitors or beta-blockers

Hemodynamic and ventriculographic findings

Left ventricular ejection fraction <20%
Concomitant right ventricular dysfunction
Pulmonary hypertension
Right atrial pressure >8 mm Hg
Pulmonary capillary wedge pressure >20 mm Hg
Cardiac index <2.0 L/min/m^2

Neurohormonal abnormalities

Hyponatremia (serum sodium <137 mmol/L)
Enhanced sympathetic tone (elevated plasma norepinephrine or resting sinus tachycardia)
Persistent elevation of BNP or troponin

Histologic features

Active granulomatous myocarditis on endomyocardial biopsy

Arrhythmia pattern

History of prior cardiac arrest
Symptomatic or asymptomatic nonsustained runs of ventricular tachycardia
Second- or third-degree AV block

NYHA, New York Heart Association; S_3, third heart sound; ACE, angiotensin-converting enzyme; AV, atrioventricular.

III. HYPERTROPHIC CARDIOMYOPATHIES

A. Background.

1. Hereditary condition characterized by LV hypertrophy, hyperdynamic systolic function, and markedly impaired diastolic function.
2. HCM should be differentiated from hypertensive concentric left ventricular hypertrophy (LVH), which is commonly seen in elderly hospitalized patients.
3. Clinical manifestations.
   a. Dyspnea on exertion (secondary to impaired diastolic filling and elevated filling pressures) is the most frequent symptom.
   b. Angina-like chest pain (due to increased LV mass, wall stress, and concomitant atherosclerotic coronary artery disease in older patients) may occur.
   c. Syncope and near syncope (due to outflow tract obstruction, ventricular arrhythmias, or inadequate diastolic filling) are uncommon.

B. Pathophysiology.

1. HCM is inherited in >60% of cases as autosomal dominant trait.
2. Specific single-point mutations in genes that encode key sarcomeric contractile and regulatory proteins (e.g., β-myosin heavy chain, troponin T, myosin binding protein, and tropomyosin) cause this disease phenotype.
3. Pathologic hallmark = unexplained myocardial hypertrophy; intraventricular septum typically >> ventricular free wall, but concentric LVH can also occur.
4. HCM may have obstructive or nonobstructive physiology, depending on the presence/absence of dynamic subaortic outflow tract pressure gradients.
5. Physical findings are dependent on presence/absence of outflow tract obstruction, its severity, and the presence/absence of mitral regurgitation (MR).
   a. Precordial palpation typically reveals a hyperdynamic systolic apical impulse.
   b. Carotid upstoke is very rapid; if obstruction occurs, a bisferiens character (rapid initial upstroke, slow second carotid impulse) may be palpable.
   c. Prominent S4 gallop is virtually always present, in presence of sinus rhythm.
   d. Systolic murmur(s) may be due to outflow obstruction and/or MR.
   e. Bedside maneuvers help differentiate HCM from aortic stenosis or MR (Table 26-5).

C. Diagnosis.

1. ECG generally demonstrates.
   a. LVH with strain pattern.
   b. "Pseudo-MI pattern": QS waves due to marked LV hypertrophy.
2. Echocardiogram is the most useful diagnosis tool.
   a. Asymmetrical hypertrophy of the intraventricular septum with septal-to-ventricular free wall ratio ≥1.3:1 is highly suggestive.
   b. Doppler interrogation at rest and during provocative maneuvers (PVCs, Valsalva) is critical to assess presence/severity of dynamic outflow obstruction and presence/absence of MR.

TABLE 26-5 Bedside Maneuvers to Differentiate the Murmur of Obstructive HCM from That of Valvular Heart Disease

	Response of murmur		
Maneuver	**HCM**	**Aortic stenosis**	**MR**
Hypovolemia Tachycardia Valsalva Venodilators (nitrates) *(decreased LV cavity size)*	Increased	Decreased	Decreased
Volume expansion Passive leg elevation Isometric hand grip Vasopressors *(increased cavity size)*	Decreased	No change or small increase	No change or small increase

HCM, hypertrophic cardiomyopathy; LV, left ventricular.

D. Treatment.

1. Noncompliant LV is poorly equipped to handle sudden preload shifts.

2. Hypovolemia will worsen dynamic outflow obstruction and increase the degree of MR.

3. Transesophageal echocardiogram (TEE) or continuous hemodynamic monitoring is recommended for patients with marked LV hypertrophy and/or significant outflow tract obstruction (>50 mm Hg) undergoing surgical procedures associated with

a. Significant blood loss.

b. Marked decrease in vascular tone.

c. Anticipated need for transient inotropic support.

4. Pharmacologic therapy.

a. Diuretics should be used judiciously for acute volume overload.

b. β-Blockers are most frequently utilized in patients with symptomatic HCM (Fig. 26-1).

i. High doses are often required.

ii. Sustained-release preparations should be replaced with shorter-acting agents during periods of hemodynamic lability.

c. Calcium channel blockers, particularly verapamil, are useful in patients with persistent symptoms or intolerance to β-blockers.

d. Catecholamines, particularly beta-agonists like dobutamine, should be avoided whenever possible as they will increase dynamic outflow obstruction.

e. Atrial fibrillation management may include:

i. β-Blocker or calcium blocker for rate control.

ii. Intravenous amiodarone.

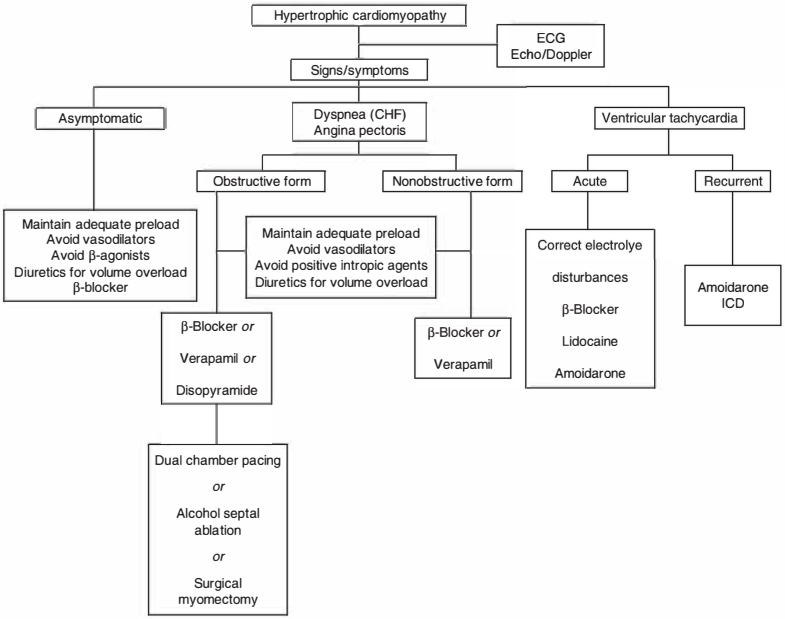

Figure 26-1: Treatment algorithm for the management of patients with known HCM. ECG, electrocardiogram; CHF, congestive heart failure; ICD, implantable cardioverter defibrillator.

iii. Prompt cardioversion if poorly tolerated.
iv. Systemic anticoagulation (very high risk of emboli).

f. Surgical septal myectomy or alcohol septal ablation improves symptoms for patients with NYHA class III or IV angina or dyspnea and marked outflow tract obstruction despite optimized pharmacologic therapy.

E. Prognosis.

1. High-risk patients can be identified by clinical, ECG, and echo features and may require consideration of defibrillator implantation.
a. Age < 30 years at diagnosis.
b. Family history of HCM and sudden cardiac death.
c. History of syncope.
d. Nonsustained ventricular tachycardia on ECG monitoring.
e. Marked LVH (wall thickness >30 mm).
f. Fall in blood pressure during exercise testing.

IV. RESTRICTIVE CARDIOMYOPATHIES

A. Background.

1. Least common type (<5%) of heart muscle disease.
2. Hallmarks include:
a. Severe diastolic dysfunction (restrictive echo pattern).
b. Normal systolic function and cavity size.
c. Substantial biatrial enlargement.

3. Common etiologies to consider: amyloidosis, hemochromatosis, idiopathic, and radiation-related endomyocardial fibrosis.

B. Pathophysiology.

1. Ventricular myocardium is rigid and noncompliant, resulting in elevated filling pressures.
2. Clinical and hemodynamic features often mimic constrictive pericardial disease.
3. Heart failure is the most common clinical manifestation.
4. Physical finding may include:
   a. Increased jugular venous pressure (JVP) and prominent Y descent.
   b. + Kussmaul sign.
   c. Moderate (1–2/6) MR/TR murmurs.

C. Diagnosis.

1. Evaluation centers on differentiating (a) RCM from constrictive disease and (b) idiopathic disease from infiltrative disease etiologies.
2. Echocardiography will typically show
   a. Concentric LVH and normal ventricular size.
   b. Biatrial enlargement.
   c. Doppler evidence of restrictive physiology on transmitral inflow (i.e., prominent E wave, short isovolumetric relaxation time, and short deceleration time) (Fig. 26-2).
3. Increased myocardial echogenicity ("speckling") suggests an infiltrative process such as amyloidosis, which can be confirmed by
   a. Rectal biopsy (70% sensitivity).
   b. Abdominal fat pad biopsy (80% sensitivity).
   c. Endomyocardial biopsy (>99% sensitivity).

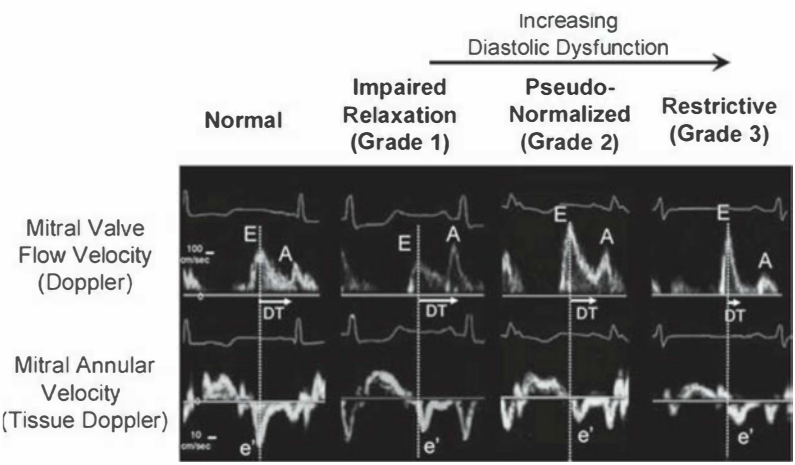

Figure 26-2: Restrictive filling pattern on transmitral Doppler echocardiography. **Top panel**: mitral valve flow velocity (Doppler); **Bottom panel**: mitral annular velocity (tissue Doppler); DT: deceleration time. (Used with permission from Little WC, Oh J. Echocardiography evaluation of diastolic function can be used to guide clinical care. *Circulation* 2009;120:803.)

4. Cardiac MR or high-resolution CT imaging should be performed to exclude pericardial constriction if diagnosis remains uncertain based on clinical and/or hemodynamic features.

D. Treatment.

1. General measures should include:
   a. Low doses of diuretics to decrease "congestive" symptoms.
   b. Pulmonary capillary wedge (PCW) should generally exceed 15 mm Hg if hemodynamic monitoring is undertaken to avoid inadequate preload during periods of instability.
   c. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers are generally ineffective and should be avoided during hospitalization.
2. Cardiac amyloidosis may respond to
   a. Prednisone and melphalan immunosuppression.
   b. Heart transplantation followed by autologous bone marrow transplantation.
3. Atrial fibrillation is poorly tolerated and may require urgent cardioversion and initiation of amiodarone or β-blocker treatment.

E. Prognosis.

1. Cardiac amyloidosis is the disease paradigm.
   a. Cardiac involvement is common in immunologic (AL) and transthyretin types (TT).
   b. Survival <24 months from onset of heart failure symptoms.
2. Idiopathic restrictive disease.
   a. Disease of elderly.
   b. Five-year survival rate: 65%.

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27 Valvular Heart Disease

Akshay S. Desai, Michael F. Bellamy, and Maurice Enriquez-Sarano

I. AORTIC STENOSIS

A. Principles: irrespective of how acute or severe its presentation, severe aortic stenosis (AS) should always be considered a surgical disease.

B. Etiology and natural history.

1. **Etiology:** principally degenerative, with progressive, age-related calcification of normal trileaflet valve. Calcification of congenitally bicuspid valve may lead to presentation earlier in life. Rheumatic disease is increasingly less common.
2. **Progression:** on average, decrease of 0.1 cm^2/year in valve area and increase of 7 mm Hg/year in mean transvalvular gradient, but rate of progression is highly variable and difficult to predict for individual patients. Older age, renal failure, hypertension, smoking, and hyperlipidemia associated with more rapid progression.
3. **Clinical natural history:** serious without symptoms but poor once even mild symptoms occur.

C. Pathophysiology.

Progressive obstruction to left ventricular (LV) outflow, characterized by increased transvalvular velocity and pressure gradient and reduced effective aortic orifice. High afterload leads to compensatory, concentric LV hypertrophy, diastolic dysfunction, enhanced wall stress, and ultimate failure due to "afterload mismatch." Timely intervention to relieve the mechanical obstruction often reverses ventricular dysfunction. Gradient is determined by valve area but also flow and aortic compliance, so that discordance among gradient–valve area is frequent.

D. Clinical presentation.

1. **Acute presentation:** chest discomfort (angina), syncope, or heart failure.
2. **Prognosis:** average survival 1 to 3 years from symptom onset without surgical intervention.
3. **Clinical examination:** slow rising, late-peaking, low-amplitude carotid pulse (*parvus et tardus*). Harsh, late-peaking basal systolic ejection murmur and decreased (or absent) aortic component of S2; radiation of murmur to apex may mimic mitral regurgitation (MR) (Gallavardin phenomenon). Murmur may be diminished or absent in patients with reduced ejection fraction (EF) and progressive LV failure.

E. Investigations.

1. Electrocardiogram (ECG) and chest radiograph: LV hypertrophy nonspecific and not always present.

2. Echocardiography.
   a. **Two-dimensional echocardiography** defines valve anatomy and calcification, LV hypertrophy, and systolic function.
   b. **Doppler echocardiography** measures transaortic jet velocity, pressure gradient, and effective aortic orifice area (severe if 4 m/s or greater, 40 mm Hg [mean] or greater, and <1.0 cm^2, respectively). Gradient is often low despite tight valve area, even with normal LV function, requiring additional testing.
   c. Patients with suspected AS, severe LV dysfunction, and low cardiac output (and hence low transvalvular pressure gradient) may benefit from dobutamine stress to clarify severity. With dobutamine, "true" severe AS gradient increases with unchanged valve area. Contractile reserve (>20% increase in stroke volume with dobutamine) predicts better outcome following aortic valve replacement (AVR), but AVR should not be denied to severe AS even without contractile reserve.
3. Computed tomography measures the large amount of aortic valve calcium in severe AS and permits evaluation of aortic root dimensions.
4. Cardiac catheterization verifies severity of AS in difficult cases and provides preoperative coronary angiography.

F. Management.

1. Intensive care unit management: cautious use of diuretics for heart failure to avoid excessive hypovolemia. Support blood pressure by all means in hypotensive patients. Caution with use of vasodilators, given propensity for hypotension (limited ability to augment cardiac output).
2. AVR, typically with surgery, is the lifesaving intervention. For patients with bicuspid aortic valve and ascending aortic dilation, concomitant ascending aortic replacement may be necessary.
3. Transcatheter aortic valve replacement (TAVR) is a reasonable alternative to surgical valve replacement for symptomatic patients with severe AS deemed inoperable or high risk for surgery.
4. Percutaneous intervention with balloon valvuloplasty is rarely useful, except as a palliative measure (risky and only transiently effective) or in patients with associated severe obstructive pulmonary disease to triage the AS component of dyspnea.

II. AORTIC REGURGITATION

A. Etiology: primary valvular aortic regurgitation (AR) may be a sequela of endocarditis, bicuspid aortic valve, rheumatic heart disease, or valvular prolapse. It may also present as secondary complication of aortic root disease, aortic dissection, or aortic trauma. Chronic AR of any cause may present acutely with heart failure.

B. Pathophysiology: over time, chronic AR leads to both increased preload (increased end-diastolic volume) and increased afterload (increased systolic pressure and wall stress) with associated eccentric ventricular hypertrophy and LV cavity dilation. Progressive rise in end-systolic wall stress ultimately results in afterload mismatch, decline in systolic function, and heart failure.

Acute, severe AR abruptly reduces ventricular compliance, generating high filling pressures and heart failure despite low-intensity murmur.

C. Clinical presentation.

1. Symptoms: exertional dyspnea and heart failure; angina prominent late in course.
2. Physical examination: classically, wide pulse pressure reflecting large stroke volume, with associated diastolic decrescendo murmur at the base. Severity of AR correlates better with duration than intensity of murmur. Chronic, severe AR may be associated with a number of characteristic signs or arterial hyperpulsatility on physical examination including a "water hammer" (Corrigan) pulse, capillary pulsations (Quincke sign), and a variety of other auscultatory findings of wide pulse pressure. Functional mitral stenosis (MS) may be audible as an apical diastolic rumble (Austin-Flint murmur). Acutely, these signs may be absent, and the diastolic murmur is often unimpressive or short due to rapid equalization of aortic and LV end-diastolic pressures.

D. Investigations.

1. ECG and chest radiograph: Acutely, pulmonary edema may contrast with normal heart size and lack of ventricular hypertrophy. Chronic AR is associated with prominent ventricular enlargement (*cor bovinum*). Severe aneurysmal dilation of the aorta may suggest primary disease of the aortic root as a mechanism for AR.
2. Echocardiography.
   a. May be helpful in evaluation of leaflet anatomy and motion as well as size and shape of the aortic root, to identify the cause of AR. Ventricular chamber dimensions, volumes, EF, and mass can also be assessed. Transesophageal echocardiography (TEE) may provide more detailed assessment where transthoracic imaging is inadequate.
   b. Doppler and color-flow imaging show the regurgitant jet. AR may be quantified by calculating the effective regurgitant orifice area and regurgitant volume (severe if ≥ 0.30 cm^2 and ≥ 60 mL/beat, respectively).
3. Cardiac catheterization: may permit assessment of AR severity by aortography and coronary angiography may be performed in older patients (if no large vegetations) as a prelude to surgical intervention.

E. Management.

1. Afterload reduction with intravenous or oral vasodilators is central to the acute medical treatment of severe AR. Intra-aortic balloon counterpulsation and β-blockade are contraindicated.
2. Surgical valve replacement is indicated in chronic AR for symptomatic patients and those with evidence of LV dysfunction (EF $\leq$ 55%) or severe LV cavity dilation (end-diastolic dimension $\geq$75 mm Hg, end-systolic dimension $\geq$55 mm or $\geq$25 mm/m^2). Valve replacement may be urgently required in patients with acute, severe AR, and heart failure. Aortic valve repair is sometimes possible. Periannular repair is necessary for perivalvular abscesses in patients with endocarditis.

3. For patients with AR secondary to aortic root disease, progressive aortic enlargement (beyond 50 mm in those with a bicuspid valve and beyond 55 mm in those with a tricuspid valve) may be an independent indication for surgical intervention to prevent rupture. In some patients, a structurally normal aortic valve may be preserved during surgical repair or replacement of the enlarged aortic root.

III. MITRAL REGURGITATION

A. Etiology and mechanism.

1. **Primary mitral valve (MV) disease:** due most commonly to myxomatous degeneration (e.g., MV prolapse), rheumatic heart disease, infective endocarditis, or annular calcification.
2. **Ischemic or functional MR:** most commonly due to valve tenting, secondary to chordal traction following progressive ventricular remodeling in patients with cardiomyopathy or previous myocardial infarction. Rarely a consequence of acute papillary muscle rupture, for example, following acute myocardial infarction.

B. Pathophysiology.

1. Chronic, severe MR increases LV end-diastolic volume and promotes progressive eccentric hypertrophy, further distortion of the papillary muscle architecture, and additional MR. Progressive volume loading, with attendant rises in wall stress, overwhelms compensatory mechanisms and leads to myocardial failure.
2. Acute onset of severe MR (e.g., in the context of myocardial infarction with papillary muscle rupture or endocarditis with leaflet perforation) causes a marked reduction of forward stroke volume and abrupt increase in end-diastolic volume. In contrast to chronic MR, the regurgitant volume is tolerated poorly due to small left atrial (LA) size with diminished LA compliance. Abrupt rise of LA pressure leads to pulmonary edema, marked elevation of pulmonary vascular resistance, and biventricular heart failure.

C. Clinical presentation.

1. Symptoms.
   a. Nature and severity of symptoms are related to the severity of the MR, its rate of progression, the levels of filling pressures, and the presence of atrial arrhythmias or associated valvular, myocardial, or coronary artery disease.
   b. Exertional dyspnea and symptoms of low cardiac output (weakness, fatigue) are common in patients with chronic, severe MR.
   c. Patients with acute, severe MR typically present with the abrupt onset of pulmonary edema in a suggestive clinical context (e.g., acute myocardial infarction, endocarditis). Hypotension and frank cardiogenic shock may develop, requiring urgent or emergent surgical intervention.
2. Physical examination: classically, apical holosystolic murmur radiating to the left axilla and infrascapular area (though anterior radiation

may occur with posterior leaflet problems). P2 component of S2 may be increased if associated pulmonary hypertension is present. S3 and S4 gallops are frequently audible. Diastolic rumble may occasionally be audible in severe MR (functional MS). Murmur of acute MR may be lower pitched and softer than the murmur of chronic MR.

D. Investigations.

1. ECG and chest radiograph: In chronic MR, principal ECG findings are LA enlargement and, frequently, atrial fibrillation (AF). Chest radiography reveals cardiomegaly with LV and LA enlargement. In acute, severe MR, atrial enlargement and cardiomegaly are often absent.
2. Echocardiography and Doppler.
   a. Two-dimensional (2D) echocardiography provides important clues to (i) etiology and mechanism (e.g., ruptured chord or papillary muscle) and (ii) ventricular function, global and regional. Given its superior ability to assess the detailed anatomy of the MV and severity of regurgitation, TEE is often useful when transthoracic images are suboptimal. Live three-dimensional echocardiography shows the entire valve anatomy.
   b. Doppler and color flow show the jet and direction (septal-superior for posterior leaflet, lateral for anterior leaflet, central for functional or bileaflet) and quantify MR (effective regurgitant orifice, regurgitant volume, severe if ≥ 0.40 cm^2 and ≥ 60 mL/beat, respectively).
3. Cardiac catheterization can help verify the severity of MR, hemodynamics, and LV function but mostly is used to assess coronary lesions and need for revascularization.

E. Management.

1. Medical treatment.
   a. Pharmacologic therapy with vasodilators is generally ineffective for management of chronic severe MR since afterload is not excessive. Without surgical treatment, prognosis for patients with severe MR and heart failure is poor.
   b. Surgical treatment should be considered for patients with symptoms or functional disability related to MR or for asymptomatic patients with progressively deteriorating LV function or increasing chamber dimensions.
   c. Acute severe MR may require medical stabilization with afterload reducing agents (e.g., nitroprusside), inotropes (e.g., dobutamine), or intraaortic balloon counterpulsation. Diuretics, nitrates, and mechanical ventilation may be useful in the management of associated pulmonary edema.
2. Surgical treatment.
   a. Outcome depends on clinical and hemodynamic status of patient, age of patient, comorbidities, and skill/experience of surgical team. It is also strongly influenced by severity of LV dysfunction and presence of concomitant coronary artery disease. Recent decreases in operative mortality allow consideration of surgery even in elderly patients or those with advanced heart failure.

b. Approach varies according to mechanism. MV repair preferred to replacement where possible; repair typically possible in those with degenerative disease or leaflet perforation, but more difficult in those with significant rheumatic deformity or calcification of the subvalvular apparatus.

c. Hemodynamic stabilization with medical therapy is optimal before surgical intervention, but emergent surgical intervention may be indicated (despite high perioperative mortality) for those with acute papillary muscle rupture and shock or for infective endocarditis complicated by refractory congestive heart failure or recurrent emboli.

IV. MITRAL STENOSIS

A. Etiology: predominantly rheumatic.

B. Pathophysiology: The fixed orifice due to commissural fusion leads to large gradient with increases in flow (pregnancy, anemia) and to heart failure.

C. History: Most commonly, presenting symptoms are fatigue, dyspnea, and diminished effort tolerance. Usually a slowly progressive disease, though those with critical MS may experience attacks of sudden pulmonary edema precipitated by AF, pregnancy, fever, effort, or other physical/emotional stress. Some experience sequelae of severe pulmonary hypertension (chest pain, hemoptysis) and massive LA remodeling (peripheral emboli, compression of recurrent laryngeal nerve).

D. Physical examination: typically, irregular pulse secondary to AF with signs of left and right heart failure. Characteristic auscultatory features include accentuated S1 with opening snap and low-pitched apical diastolic rumble (best heard in left lateral decubitus position). Parasternal (right ventricular [RV]) lift, accentuation of P2, and narrowed splitting of second heart sound are notable as pulmonary hypertension develops. S3 absent unless significant MR or AR coexists. Of note, diastolic murmur sometimes is inaudible in low-flow MS of the elderly.

E. Investigations.

1. ECG and chest radiograph: LA enlargement is usually present in sinus rhythm; AF common with progressive disease; RV hypertrophy may develop in setting of associated pulmonary hypertension. Chest radiograph frequently demonstrates evidence of LA enlargement (occasionally severe) and may rarely show MV calcification.

2. Echocardiography and Doppler.

a. 2D echocardiography for (i) assessment of MV anatomy, (ii) planimetry of reduced orifice, and (iii) quantification of valvular and subvalvular calcification with scoring to assess suitability for balloon valvuloplasty.

b. Doppler echocardiography and color flow for (i) assessment of MS severity (mean transmitral gradient and valve area, severe if ≥10 mm Hg or ≤1.5 cm^2, respectively) at rest and with exercise, (ii) identification of associated MR, and (iii) assessment of hemodynamics

(pulmonary hypertension, filling pressures) and evaluation of aortic valve (affected in approximately one-third of patients with MS).

c. TEE: may provide additional information regarding (i) LA (appendage) thrombus and (ii) MR presence and severity.

3. Cardiac catheterization: permits detailed hemodynamic assessment of the MV (usually necessary only when echocardiography is nondiagnostic) and coronary angiography. Most commonly done in tandem with an attempt at percutaneous balloon mitral valvuloplasty.

F. Management.

1. Acute management of heart failure symptoms may include oxygenation, diuretics, β-blockers/calcium channel blockers for control of heart rate, and mechanical ventilation. Warfarin anticoagulation should be considered for prevention of systemic embolism in patients with AF, prior embolic events, and those with known LA thrombus.

2. Surgical or percutaneous intervention should be considered in patients with severe, symptomatic MS, or those with moderately severe MS and new-onset AF or significant pulmonary hypertension.

3. In patients with favorable valve morphology, mild MR, and no evidence for LA thrombus, percutaneous balloon mitral valvuloplasty is the preferred treatment with results equivalent to surgical commissurotomy; can be done in pregnant women with low risk.

4. Surgical MV repair/replacement reserved primarily for those with heavily calcified valves or with significant concomitant MR who are not candidates for a percutaneous procedure.

V. PROSTHETIC VALVE COMPLICATIONS

A. Prosthetic valve thrombosis.

1. Clinical presentation: stroke due to systemic embolism or heart failure due to obstruction of a mechanical heart valve. Suspect in patients with new dyspnea in association with muffled valve closure sounds or new murmurs on auscultation.

2. Investigations: echo to assess severity of prosthetic obstruction; transesophageal echo may be useful to better define thrombus size and degree of limitation in movement of mobile element. Fluoroscopy may provide superior visualization of valve leaflets due to acoustic shadowing on ultrasound.

3. Treatment.

a. Reoperation: preferred for left-sided valve thrombosis with symptomatic heart failure and large clot burden.

b. Thrombolysis: risk of embolism and secondary recurrence, but reasonable to consider for poor surgical candidates or as primary therapy for those with right- or left-sided valve thrombosis with small clot burden and mild symptoms. Fibrinolytic therapy with streptokinase or recombinant tissue plasminogen activator (r-TPA) followed by intravenous heparin and aspirin until international normalized ratio (INR) is therapeutic.

B. Prosthetic valve endocarditis.

1. Clinical presentation: infection, embolism, or heart failure. May affect both mechanical and bioprosthetic valves.
2. Investigations: Blood cultures and TEE are key to diagnosis. TEE also shows abscesses, fistula, and intraprosthetic and periprosthetic regurgitation.
3. Treatment antibiotics: early reoperation to remove infected tissue and foreign material, especially if heart failure is present.

C. Structural failure.

1. Bioprosthesis: frequent, progressive due to degeneration. Reoperation after stabilization.
2. Mechanical valve: rare, sudden due to defective material. Urgent reoperation.

D. Prosthetic regurgitation.

1. Presentation: heart failure or anemia due to hemolysis. Murmur may not be audible.
2. Investigations: Echocardiography, particularly TEE, is key to diagnosis.
3. Treatment by reoperation (urgency determined by severity of heart failure and infectious cause). Percutaneous treatment of periprosthetic regurgitation is possible.

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28 Critical Care of Pericardial Disease

Andrea Loiselle and Sunil Mankad

I. GENERAL PRINCIPLES

A. Definition.

There is a wide spectrum of pericardial disease seen in critical care, but the clinicopathologic processes involved are relatively few and include the following:

1. Pericarditis, with or without pericardial effusion and with or without myocardial involvement (myopericarditis).
   - **a.** Acute.
   - **b.** Subacute.
   - **c.** Chronic, fibrinous, noneffusive, or exudative.
2. Pericardial effusion and cardiac tamponade.
3. Constrictive pericarditis.
   - **a.** Acute.
   - **b.** Subacute.
   - **c.** Chronic adhesive.
   - **d.** Fibrocalcific.

B. Anatomy.

1. The pericardium is a double-layered fibroserous sac that surrounds the heart and is made up of a ***visceral*** layer that adheres firmly to the epicardium and a tough, fibrous outer ***parietal*** layer.
2. Importantly, the pericardium reflects over the origin of the great vessels; therefore, a hemorrhagic pericardial effusion may develop with ascending aortic dissection/rupture.
3. A small amount of fluid (up to 50 mL) normally exists between these two pericardial layers in the ***pericardial space***, and there is enough slack in the parietal pericardium to usually accommodate 100 to 200 mL of fluid before causing hemodynamic compromise.
4. Histologically, the pericardium is made up of compact collagen layers interspersed with elastin fibers, which help provide mechanical viscoelastic function.

C. Etiology (of pericarditis with or without effusion).

1. Idiopathic.
2. Infectious (viral or bacterial).
3. Related to myocardial infarction.
4. Secondary to connective tissue disease/vasculitis.
5. Immunopathic or associated with "hypersensitivity" states including post cardiotomy related.

6. Secondary to diseases of contiguous structures.
7. Secondary to disorders of metabolism.
8. Neoplastic.
9. Traumatic.
10. Radiation induced.
11. Uremic.

D. Pathophysiology.

1. The unique anatomy of the pericardium allows for the pressure–volume relation of the pericardium to be nonlinear, with an initially flat response (little change in pressure despite large changes in volume) and a subsequent "threshold" critical volume at which point a steep slope develops (large change in pressure with small changes in volume).
2. The pericardium serves several important functions although it is not essential for life and its congenital absence or surgical removal leads to no major clinical problems.
   a. The pericardium limits distention of the cardiac chambers.
   b. This facilitates interaction, interdependence, and coupling of the ventricles and atria such that changes in pressure/volume in the right heart influence pressure/volume in the left heart and *vice versa*.
   c. The normal thin-walled right ventricle is usually affected more by this restraint than is the thick-walled left ventricle.
3. Excessive fluid in the pericardium increases the normal pericardial effect on ventricular interaction and exaggerates the normal inspiratory decrease in systemic blood pressure, thereby leading to pulsus paradoxus (inspiratory drop in blood pressure >10 mm Hg).
4. Although pulsus paradoxus is the hallmark of tamponade, it can be seen in other disorders, including obstructive lung disease (including severe asthma), pneumothorax, pulmonary embolism, tense ascites, obesity, mitral stenosis with right heart failure, right ventricular infarction, hypovolemia, and cardiogenic shock.
5. Beyond pericardial stretch, compensatory mechanisms for tamponade are mainly adrenergically mediated, including tachycardia, peripheral vasoconstriction, and maintained ejection fraction (in pure tamponade without heart disease, the ejection fraction is normal or increased); eventually, these compensatory mechanisms fail and cardiac output or stroke volume fall.
6. Like tamponade, constriction severely limits ventricular filling, with equalization of left and right heart diastolic pressures; systolic right ventricular pressure rises but usually to <50 mm Hg, and the ratio of right ventricular end-diastolic pressure to systolic pressure is usually >0.3.
7. Unlike in cardiac tamponade, the heart is not compressed in early diastole and relaxes normally or abruptly (rubber bulb effect) as filling proceeds until it reaches its pericardial limit.

II. PERICARDITIS

A. Diagnosis.

1. Acute pericarditis may be asymptomatic, but more often the patient has central, sharp, positional (worse when patient is supine and reduced

when patient sits up) chest pain with a pleuritic component; however, chest pressure that may approximate angina may also occur.

2. Chest pain may migrate to anywhere in the chest but frequently radiates to one or both of the trapezius ridges.
3. True dyspnea does not occur in the absence of a large pericardial effusion, but shallow, rapid breathing due to pleurisy is often present.
4. Odynophagia (pain on swallowing) occasionally occurs.
5. The pericardial friction sound (rub) is pathognomonic but varies from faint to very loud (especially in uremic pericarditis) and may be transient; a fully developed rub has three components: atrial late diastolic rub, ventricular systolic rub, and an early diastolic rub.
6. The white blood cell count, sedimentation rate, and other acute phase reactants vary according to the etiologic agent or primary illness; serum levels of cardiac enzymes vary, depending on coexistent myocardial involvement (myopericarditis).
7. Acute pericarditis is most often an inflammatory, fibrinous disease without an increase in the normal amount of pericardial fluid; cardiomegaly on chest radiography will occur only if >200 to 250 mL of pericardial fluid has accumulated.
8. Typically, four potential electrocardiographic (ECG) stages are noted, with the entire ECG evolution occurring in a matter of days or weeks.
   a. Stage I (Fig. 28-1): diffuse concave upward ST (J-point) elevation with ST depression in lead AVR consistent with epicardial inflammation.
   b. Stage II: ST (J) segments return to baseline more or less "in phase," with little change in T waves. The PR segments may be depressed in either stage I or, more often, stage II and rarely in stage III. T waves progressively flatten and invert in all or most of the leads that showed ST segment elevations.

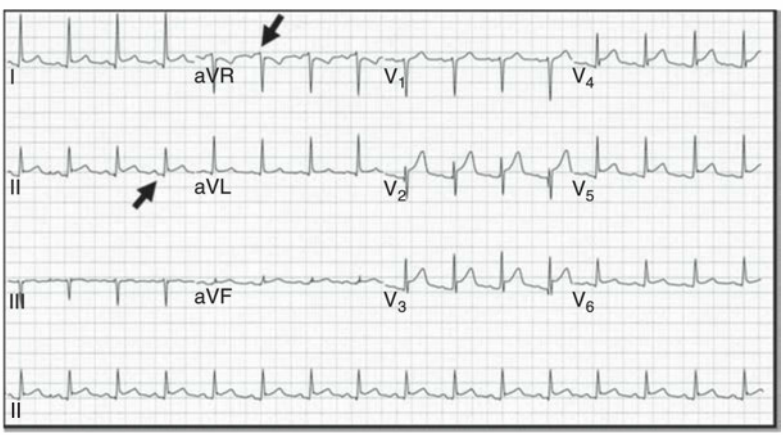

Figure 28-1. Shown are the characteristic ECG stage I findings of acute pericarditis including diffuse concave upward ST (J-point) elevation in leads I, aVL, aVF, V_2, V_2–V_6 with ST depression in lead accelerated ventricular rhythm (AVR) consistent with epicardial inflammation; also shown is PR segment depression/elevation in leads II and aVR, respectively (*black arrows*).

c. Stage III: T-wave inversions appear and are not distinguishable from those of diffuse myocardial injury, myocarditis, or biventricular injury.
d. Stage IV: T waves return to their prepericarditis configuration.

B. Treatment.

1. The treatment of clinically noneffusive pericarditis or pericarditis without a compressing effusion is symptomatic and aimed at reducing pain, malaise, and fever.
2. Initial treatment is usually with nonsteroidal anti-inflammatory drugs (NSAIDs) usually resulting in prompt pain relief; typical regimens include ibuprofen (400 to 800 mg every 8 hours) or indomethacin (25 to 50 mg every 6 hours); aspirin (up to 900 mg every 6 hours) may be utilized if there is no response to the NSAIDs.
3. Intractable pericarditis may be treated with corticosteroid therapy but at the lowest dose possible with appropriate tapering; however, this may lead to chronic recurrent pericarditis symptoms with attempts at weaning.
4. For postmyocardial infarction pericarditis, steroids and NSAIDs should not be utilized due to experimental work demonstrating reduced coronary blood flow, increased myocardial infarction size, increased blood pressure, and increased incidence of myocardial rupture.
5. Colchicine 0.6 mg once or twice by mouth daily may have a role in the prevention of recurrent pericarditis. Its major adverse effect is gastrointestinal intolerance.

III. PERICARDIAL EFFUSION AND CARDIAC TAMPONADE

A. Diagnosis.

1. Noncompressing effusions may produce no clinical manifestations and may be the only sign of pericardial disease; if a systemic or extrapericardial disease is responsible for the pericarditis, signs and symptoms of that condition may dominate the picture.
2. Extremely large noncompressing effusions may produce precordial discomfort and symptoms resulting from pressure on adjacent structures, such as dyspnea (from reduced lung capacity), cough, hoarseness, dysphagia, and hiccups; heart sounds may be muffled with massive effusions.
3. The ECG may show low-voltage QRS complex and T waves with nearly always normal P-wave voltage; electrical alternans may be present (Fig. 28-2).
4. Cardiac tamponade is defined as hemodynamically significant cardiac compression resulting from accumulating pericardial contents that overcome compensatory mechanisms and must be considered in any patient with cardiogenic shock and venous congestion; the pericardial effusion may be fluid, blood, pus, or gas (including air).
5. Cardiac tamponade may appear insidiously as the first sign of pericardial injury or intrapericardial bleeding, especially in conditions such as neoplasia, trauma, and connective tissue disorders.

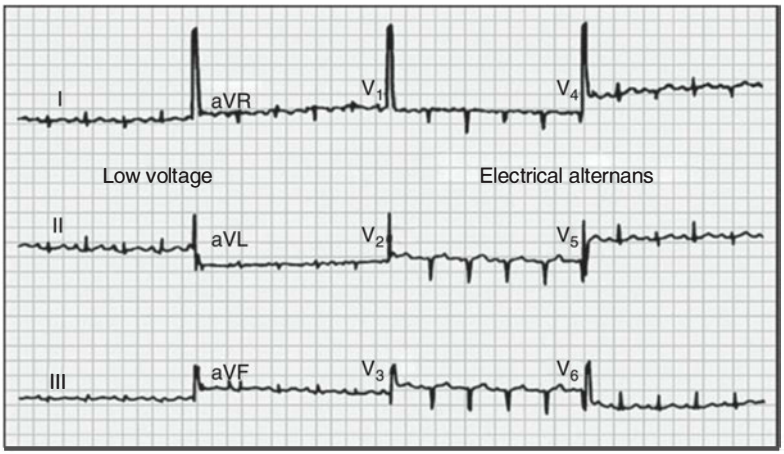

Figure 28-2. Shown is a typical electrocardiograph (ECG) in a patient with a large pericardial effusion; the limb leads *show* low voltage and electrical alternans (beat-to-beat change in QRS axis) is demonstrated in leads aVR, V_1, V_4, and V_5.

6. Most patients are hypotensive and tachycardic; in patients with rapid tamponade, such as procedural-related perforation or hemorrhage, the dominant picture is one of shock.
7. Heart sounds may be distant; neck veins are typically engorged, even with the patient sitting erect; forehead, scalp, and retinal venous engorgement are common.
8. If the jugular venous pattern can be discerned, a single negative systolic phase in mid-systole, x descent, with absence of the y descent can be a valuable finding (Fig. 28-3).
9. *Pulsus paradoxus* occurs when respiratory changes alternatively favor right and then left heart filling; however, left ventricular hypertrophy and/or hypovolemia may mask this finding.
10. Echocardiography plays a pivotal role in the diagnosis of pericardial tamponade including:
    a. Confirmation of the presence of pericardial effusion.
    b. Documentation of chamber compression (atrial or ventricular); early diastolic right ventricular compression is a specific finding.
    c. Exaggerated respiratory variation of the peak early transmitral and transtricuspid Doppler inflow velocities representing exaggerated interventricular dependence, although this may also be present in constrictive pericarditis.
    d. Focal myocardial compression, even in the absence of a large amount of pericardial fluid, may be seen postoperatively after cardiothoracic surgery or with trauma; this can easily be missed on transthoracic echocardiography, and transesophageal echocardiography may be necessary to make the diagnosis.

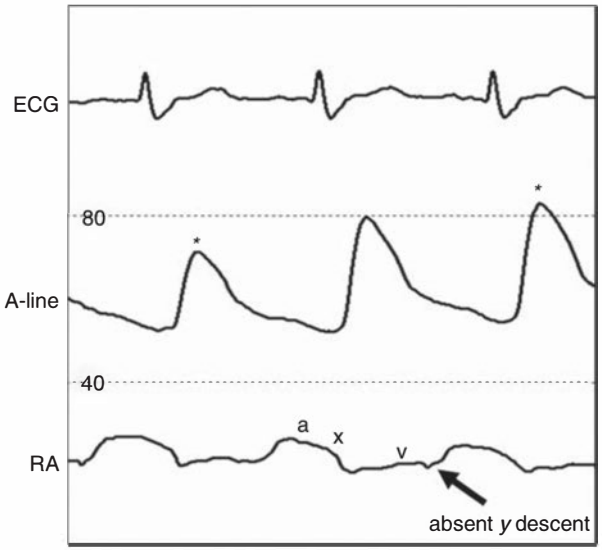

Figure 28-3. Shown are electrocardiograph (ECG), arterial line (a-line), and right atrial (RA) tracings in a patient with pericardial tamponade; note the pulsus paradoxus demonstrated on the a-line tracing (*asterisk*) as well as the blunted y descent seen on the RA trace (*black arrow*).

B. Treatment.

1. Removal of pericardial fluid as soon as possible by pericardiocentesis or surgical drainage is the definitive treatment.
2. Emergency echocardiographic-guided pericardiocentesis is a well-established, safe, effective, and readily accessible management strategy for tamponade—especially those resulting from perforation secondary to invasive catheter-based procedures; echocardiography can help establish the safest and most direct site for needle aspiration.
3. Surgical drainage is optimal for focal myocardial compression related to intrapericardial hematoma/thrombus, traumatic tamponade, or tamponade resulting from pericarditis caused by pyogenic organisms.

IV. CONSTRICTIVE PERICARDITIS

A. Diagnosis.

1. Patients usually have one or more of the following signs and symptoms of venous congestion (usually with clear lung fields) and a normal or slightly enlarged (rarely small) cardiac size.
   - **a.** Easy fatigability.
   - **b.** Dyspnea on exertion, usually with orthopnea.
   - **c.** Pedal edema, ascites, or both.
   - **d.** Hepatomegaly (and, in some cases, splenomegaly).
   - **e.** Distension of the neck veins in which the x and y descents, both are prominent venous; the y descent tends to be deeper and precipitous

as it corresponds to the ventricular pressure dip when the atrioventricular valves are open.

f. Respiratory changes in cardiac pressures are minimal, and jugular venous pressure increases during inspiration (Kussmaul sign also seen in right ventricular infarction, acute cor pulmonale, and tricuspid stenosis).

g. Inspiratory decrease in arterial pressure in pure constriction is slight, nearly always <10 mm Hg.

2. In conjunction with the clinical presentation, Doppler echocardiography can reliably confirm the diagnosis of constrictive pericarditis by illustrating exaggerated interventricular dependence; findings of a dilated inferior vena cava with decreased respiratory variation and increased expiratory diastolic flow reversals in the hepatic veins are also noted.

3. Noninvasive establishment of a thickened pericardium may also be useful using cardiac magnetic resonance or computed tomographic imaging.

4. If the diagnosis remains uncertain, simultaneous right and left heart catheterization can be performed; findings include equal and elevated right and left diastolic pressures including a "square-root" configuration to the diastolic pressure (not seen in tamponade, particularly when measured by manometer-tip catheters; Fig. 28-4); importantly, discordance of right and left ventricular pressures with respiration is seen (during peak inspiration, there is a decrease in left ventricular pressure and a concomitant increase in right ventricular pressure).

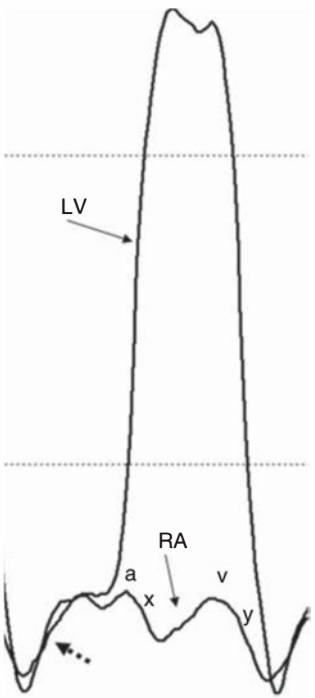

Figure 28-4. Shown are the simultaneous left ventricular (LV) and right atrial (RA) pressure curves' tracings during cardiac catheterization demonstrating the classic "dip and plateau" diastolic pressure curve (*dashed arrow*) and prominent x and y descents of the RA tracing seen in constrictive pericarditis.

B. Treatment.

1. Medical treatment of constrictive pericarditis includes diuretics for volume overload; if a significant inflammatory component is present in acute or subacute constrictive pericarditis, then a course of anti-inflammatory medications may be helpful.
2. The definitive treatment of constrictive pericarditis is surgical removal of as much of the pericardium as possible.

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29 The Acute Aortic Syndromes

Piotr Sobieszczyk

I. OVERVIEW. The acute aortic syndromes are rare yet morbid entities with variable clinical presentation. Mortality due to these disorders increases rapidly with delayed treatment, requiring a high index of suspicion to allow early recognition and management.

II. AORTIC DISSECTION

A. Background.

1. Epidemiology of aortic dissection (AD).
   a. Most common acute aortic syndrome.
   b. Estimated US annual incidence of 3.5/100,000 may be an underestimate as many patients die before diagnosis is made.
   c. Incidence increases with age.
2. Stanford classification system.
   a. Type A involves the ascending or proximal aorta.
   b. Type B involves the aorta distal to the origin of the left subclavian artery.

B. Pathophysiology.

1. Tear in the aortic intima exposes underlying media to blood flow at systemic pressure. The intimal tear propagates, forming a second or "false" lumen.
2. Etiology of AD is variable (Table 29-1). Processes that weaken the medial layers of the aorta, such as hypertension or intrinsic connective tissue disorders, may eventually result in intramural hemorrhage, AD, or rupture. Iatrogenic causes include previous aortic surgery or catheterization.

C. Prognosis.

1. Without intervention, the risk of death approaches 1%/hour in the first 24 hours after AD. For untreated cases, mortality rates are approximately 50% at 1 week and upward of 90% beyond 3 months.
2. Type A: 30-day mortality with medical management approaches 50% but 20% with surgical repair.
3. Type B: 30-day mortality rate 10% with medical therapy.

D. Diagnosis.

1. Clinical presentation is variable and depends on the aortic segment involved. No pathognomonic physical findings secure the diagnosis. Clinical index of suspicion must be high.

TABLE 29-1 Factors Associated with Predisposition to AD

Degeneration of the aortic wall
Advanced age
Chronic hypertension
Connective tissue disorders
Marfan syndrome
Ehlers-Danlos syndrome
Loeys-Dietz syndrome
Familial AD syndromes
Inflammatory disorders
Giant cell arteritis
Takayasu arteritis
Iatrogenic injury
Catheterization
Intra-aortic balloon pump
Aortic and cardiac surgery
Congenital disorders
Bicuspid aortic valve
Aortic coarctation
Turner syndrome
Noonan syndrome
Pregnancy
Cocaine use

a. Common symptoms: chest pain (73%), back pain (53%), syncope (10%).
b. Common signs: hypertension (77% type B cases, 36% type A cases).
c. Less common signs: murmur of aortic insufficiency (31%); hypotension and shock; pericardial tamponade; myocardial ischemia (3%); congestive heart failure (4% to 7%); malperfusion syndromes (e.g., limb ischemia, neurologic impairment or paraplegia, mesenteric ischemia, or renal insufficiency).

2. Diagnostic testing.
a. No reliable blood test at this time for rapid detection of AD. Elevated D-dimer may be helpful in intermediate-risk patients.
b. Chest radiography has limited diagnostic utility.
c. Electrocardiogram is nonspecific (normal in 31% of cases). Ischemic changes may be seen if type A dissection involves the coronary arteries.
d. Noninvasive imaging of the aorta establishes the diagnosis. Three available modalities provide similar diagnostic accuracy (Table 29-2). Invasive angiography is rarely required.
i. Contrast-enhanced computed tomography (CT).
ii. Transesophageal echocardiogram (TEE).
iii. Magnetic resonance angiography (MRA).

TABLE 29-2 Advantages, Disadvantages, and Performance of Aortic Imaging Modalities for AD

Modality	Findings	Advantages	Disadvantages	Sensitivity (%)	Specificity (%)
Transthoracic echocardiography	Diagnostic: Undulating intimal flap in proximal aorta Suggestive: Aortic root dilatation Aortic insufficiency Pericardial effusion	Easy to obtain Performed at bedside Noninvasive	Visualization of aorta limited to aortic root Poor image quality in many patients	70–90 (type A) 30–40 (type B)	80
Transesophageal echocardiography	Diagnostic: Undulating intimal flap in aorta Differential flow in true and false lumens Intramural hematoma Suggestive: Aortic root dilatation Aortic insufficiency Pericardial effusion	Quick to perform Performed at bedside Descending aorta can be assessed Valvular and ventricular functional assessment possible	Specially trained personnel needed to perform test Aortic arch may be obscured from overlying bronchus	90–100	70–80
CT	Diagnostic: Intimal flap within aorta Presence of dual lumens with differential contrast Enhancement Suggestive: Aortic root dilatation Pericardial effusion	Readily available at most centers	Limited visualization of branch vessels Requires intravenous iodinated contrast Unable to assess aortic valve and ventricular function	90–100	80–90
Magnetic resonance imaging	Diagnostic: intimal flap within aorta Presence of dual lumens Suggestive: Aortic root dilatation Pericardial effusion	Excellent sensitivity and specificity No need for contrast agents Assessment of branch vessels	Not uniformly available Long scanning times Difficult to monitor patients during exam	95–100	95–100
Aortography	Diagnostic: Intimal flap within aorta Presence of dual lumens Suggestive: Aortic root dilation Aortic insufficiency	Excellent branch vessel visualization	Requires assembly of angiography team Requires iodinated contrast agents Invasive Unable to detect IMH Limited sensitivity if dual lumens equally opacified	80–90	90–96

IMH, intramural hematoma.

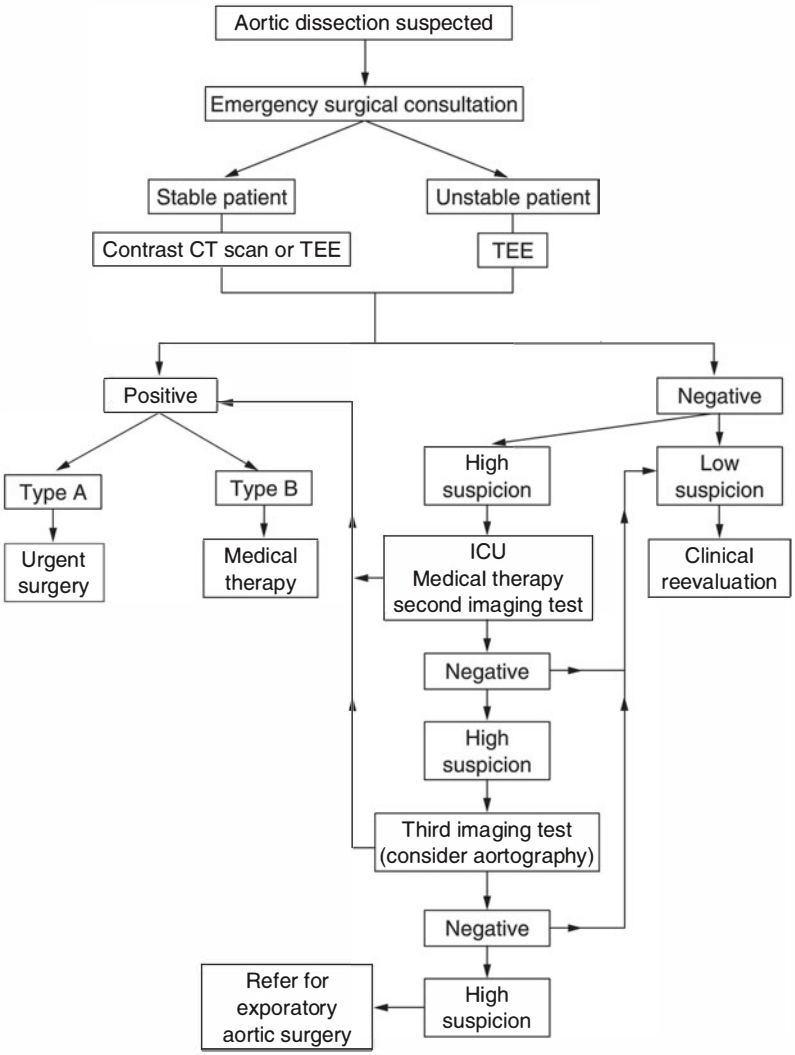

Figure 29-1. Suggested diagnostic and therapeutic algorithm for patients presenting with suspected acute AD or related entity. CT, computed tomography; TEE, transesophageal echocardiogram; ICU, intensive care unit.

E. Treatment (Fig. 29-1).

1. Early surgical consultation is critical. Initial management of hemodynamically stable patient must focus on reducing adrenergic tone and lowering heart rate and dP/dt (Table 29-3).
2. Type A dissection is a surgical emergency.

TABLE 29-3 Medical Therapy for Hemodynamically Stable Acute AD

Therapeutic goal	Medication	Suggested dose	Desired response
Pain relief	Morphine sulfate	1–2 mg IV q 3–5 min	Pain relief resulting in reduction of sympathetic tone
Heart rate reduction	Metoprolol	2.5–5.0 mg IV q 2 min up to three doses. Follow with 5–10 mg IV q 4–6 h	Maintenance of heart rate to between 60 and 70 beats per min
	Esmolol	500 μg/kg IV bolus followed by continuous infusion of 50 μg/kg/min. Titrate up to a maximum of 300 μg/kg/min.	Maintenance of heart rate to between 60 and 70 beats per min
	Propranolol	1 mg IV q 3–5 min. (not to exceed 10 mg). Follow with 2–6 mg IV q 4–6 h	Maintenance of heart rate to between 60 and 70 beats per min
Heart rate/ blood pressure reduction	Labetalol	20 mg IV over 2 min followed by 40–80 mg IV q 10–15 min to a maximum of 300 mg. Start IV infusion at 2 mg/min and titrate to 10 mg/min	Maintenance of heart rate to between 60 and 70 beats per min; maintenance of systolic blood pressure between 100 and 110 mm Hg
Blood pressure reduction	Sodium nitroprusside	0.25–0.3 μg/min IV infusion and titrate to 10 μg/kg/min	Maintenance of systolic blood pressure between 100 and 110 mm Hg
Blood pressure reduction in setting of renal artery involvement	Enalaprilat	0.625–1.25 mg IV q 6 h	Maintenance of systolic blood pressure between 100 and 110 mm Hg

3. Type B dissection is managed medically. Surgery carries high mortality and is reserved for patients with limb or visceral ischemia or contained rupture. Endovascular treatment is a viable alternative to surgery in selected high-risk patients but has not proven to be beneficial in stable patients with type B dissection.
4. Long-term management after initial stabilization requires control of hypertension; β-blocker or calcium channel blocker therapy is central to any strategy to prevent aortic expansion.

III. INTRAMURAL HEMATOMA

A. Background.

1. Intramural hematoma (IMH) comprises up to 20% of cases of acute aortic syndromes.
2. Categorized by Stanford classification system (type A and type B).

B. Pathophysiology.

1. Variant of AD.
2. Spontaneous hematoma within the medial layer of the aorta without an identifiable intimal flap. Rupture of the vaso vasorum into the medial layer is the most likely mechanism.

C. Prognosis.

1. Dependent on Stanford classification and similar to that of AD.

D. Diagnosis.

1. Clinical presentation indistinguishable from AD.
2. Pericardial effusion, hemothorax, and hemoperitoneum from rupture of the adventitia herald impending rupture.
3. Diagnosis is made by one of the imaging modalities used to diagnose AD (i.e., CT, TEE, and MRA).

E. Treatment.

1. Initial management is identical to that of AD (Fig. 29-1 and Table 29-3).
2. Surgical repair is recommended for type A IMH (surgical mortality rate of 8% vs. 55% with medical therapy).
3. Type B IMH can be managed medically but warrants careful clinical follow-up and serial imaging. Late progression of IMH to dissection, aneurysm, or rupture can be as high as 21%.

IV. PENETRATING AORTIC ULCER

A. Background.

1. Penetrating atherosclerotic ulcer (PAU) is more common in elderly patients with hypertension and severe aortic atherosclerosis.
2. Preferentially involves the descending thoracic and abdominal aorta.

B. Pathophysiology.

1. Severe atherosclerotic lesion ulcerates, penetrates through the intimal layer, and results in a discrete ulcer crater.
2. Propagation to dissection can occur but is rare: Ulceration can extend through the adventitia resulting in pseudoaneurysm formation or frank aortic rupture. Symptomatic ulcers or ulcers with deep erosion are more likely to rupture. Stable PAU will often progress to aneurysmal dilatation of the aorta.

C. Clinical presentation.

1. Occurs in patients with multiple atherosclerotic risk factors and marked systemic atherosclerosis.

2. Most patients, if they have symptoms, present with the acute onset of pain in the chest and/or the back and hypertension.
3. Pericardial tamponade, myocardial ischemia, and aortic insufficiency are uncommon because the ascending aorta is a very unusual location for PAU.

D. Diagnosis.

1. Diagnosis can be established with contrast computed tomographic angiography (CTA, TEE, or MRA).

E. Treatment.

1. Optimal treatment strategy of patients with PAU is unknown. Medical therapy is the initial choice in absence of false aneurysm formation, frank rupture, or recurrent pain.
2. Blood pressure must be controlled to reduce the shear stress and pulse pressure against the ulcer (Table 29-2).
3. Patients with hemodynamic instability, evidence of aortic rupture, or pseudoaneurysm should undergo immediate surgical therapy.
4. Elective surgical repair indicated in patients with intractable pain, distal embolization from thrombus within the ulcer or progressive aneurysmal dilatation of the aorta. Endovascular stent grafting can be used safely in selected patients.
5. Stable patients with PAU must be followed up with serial imaging studies.
6. Risk factor modification includes lipid-lowering therapy and smoking cessation.

V. RUPTURED AORTIC ANEURYSM

A. Background.

1. Annual incidence of ruptured abdominal aortic aneurysm (AAA) and thoracic aortic aneurysm (TAA) is estimated at 5 to 7 and 3.5 per 100,000 persons, respectively.
2. Owing to the progressive risk of rupture with increasing aneurysm diameter, elective repair is recommended when the diameter of the thoracic aorta reaches 6 cm (5 cm in patients with Marfan syndrome) and that of the abdominal aorta reaches 5 to 5.5 cm.

B. Prognosis.

1. Prognosis of ruptured TAA or AAA is grim. Of patients who develop rupture, 60% will die before presentation to medical attention.
2. Operative mortality for patients reaching medical attention is approximately 50%; however, mortality is 100% without surgical intervention.

C. Diagnosis.

1. Clinical presentation.
   a. Diagnosis should be considered in all patients presenting with acute hemodynamic instability and new-onset back, chest, or abdominal pain.

b. The classic triad of abdominal pain, hypotension, and a pulsatile abdominal mass is present in less than one-third of patients and supports the diagnosis of ruptured AAA.

c. Ruptured TAA can present with acute hemothorax or hemorrhagic pericardial effusion and tamponade. The most common site of rupture is in the descending thoracic aorta.

2. Diagnostic testing.

a. Imaging studies (CT or abdominal ultrasound) should be obtained only in the stable patient. If there is clinical concern of ruptured TAA or AAA in an unstable patient, immediate surgical exploration should be pursued.

D. Treatment.

1. Ruptured TAA or AAA is a surgical emergency. Immediate surgical consultation is critical for patients with symptomatic or aneurysms with suspected rupture. Endovascular repair is less morbid and is increasingly used in patients with favorable anatomy.

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30 Evaluation and Management of Hypertension in the ICU

Benjamin M. Scirica

I. DEFINITIONS

A. *Hypertensive crisis* is defined as a severe elevation in blood pressure (BP).

1. The Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High BP defines systolic blood pressure (SBP) >180 mm Hg and diastolic blood pressure (DBP) >120 mm Hg as *hypertensive crises*.
2. *Hypertensive emergencies* and *urgencies* are potentially life threatening and may occur with chronic essential hypertension, with secondary forms of hypertension, or de novo (Table 30-1).

B. *Hypertensive emergencies* and *urgencies* can be considered a continuum of disease but are differentiated by the presence or absence of acute and progressive target organ damage.

1. In *hypertensive emergencies*, BP elevation is associated with ongoing central nervous system (e.g., encephalopathy or hemorrhage), myocardial (e.g., ischemia, pulmonary edema), hematologic (e.g., hemolysis), or renal (e.g., acute renal failure) damage.
2. In *hypertensive urgencies*, the potential for organ damage is great and likely if BP is not soon controlled. These may be associated with symptoms such as headache, shortness of breath, or anxiety.

C. *Accelerated hypertension* and *malignant hypertension* traditionally referred to a hypertensive crisis with either early retinopathy (accelerated) or encephalopathy or nephropathy (malignant). These terms should not be used in current practice but rather referred to as *acute severe hypertension or hypertensive emergencies*.

II. APPROACH TO THE PATIENT

A. Immediate identification of both hypertension and potential organ damage is critical to properly triage patients. Patients with hypertensive emergencies should be admitted to an ICU setting for continuous monitoring and treatment.

B. In the ICU, therapy must often begin before a comprehensive patient evaluation is completed. A systematic approach offers the opportunity to be both expeditious and inclusive (Table 30-2).

TABLE 30-1 Examples of Hypertensive Crises and End Organ Damage

Generalized	Cardiovascular	Neurologic	Renal	Surgical
Accelerated and malignant hypertension	Acute left ventricular failure	Hypertensive encephalopathy	Acute renal failure	Postoperative hypertension
Microangiopathic hemolytic anemia/disseminated intravascular coagulation	Acute coronary syndrome	Subarachnoid hemorrhage	Acute glomerulonephritis	Postoperative bleeding after surgery
Eclampsia	MI	Intracerebral hemorrhage	Collagen vascular crisis	Severe body burns
Catecholamine excess (drugs, rebound syndrome, pheochromocytoma)	Aortic dissection	Cerebrovascular accident	End-stage renal disease	Severe epistaxis
Vasculitis				
Monoamine oxidase inhibitor interactions				

Adapted from Vidt DG, Gifford RW. A compendium for the treatment of hypertensive emergencies. *Cleve Clin Q* 1984;51:421.

TABLE 30-2 Initial Evaluation of Hypertensive Crisis in the Intensive Care Unit

1. Continuous BP monitoring
   a. Direct (intra-arterial) preferred or indirect (cuff)
2. Brief initial evaluation—history and physical examination with attention to
   a. Neurologic including fundoscopic exam, cardiac, and pulmonary system
   b. Assessment of organ perfusion and function (e.g., mental status, heart failure, urine output)
3. Blood and urine studies: electrolytes, blood urea nitrogen (BUN), creatinine, complete blood count (CBC) with differential, urinalysis with sediment; if indicated, serum catecholamines and cardiac enzymes
4. ECG (examine for LV strain or ischemia)
5. Chest radiograph (assess for size of aorta, cardiomegaly, pulmonary edema)
6. Initiation of therapy (within 1 h of presentation for *hypertensive emergencies*)
7. Further evaluation of etiology once BP is stabilized

C. A brief history and physical examination should be initiated to assess the degree of organ damage and to rule out obvious secondary causes of hypertension. The following should be assessed.

1. **History.**
   - **a.** History of hypertension or other significant medical disease.
   - **b.** Medication use and compliance.
   - **c.** Drugs of abuse or withdrawal.
   - **d.** Symptoms attributable to TOD.
     - **i.** Neurologic symptoms (headache, nausea, and vomiting; visual changes; seizures; focal deficits; mental status changes).
     - **ii.** Cardiac (chest pain, shortness of breath).
     - **iii.** Renal (hematuria, decreased urine output).
2. **Physical exam.**
   - **a.** BP readings in both arms. Intra-arterial monitoring preferred.
   - **b.** Signs of neurologic ischemia, such as altered mental status or focal neurologic deficits.
   - **c.** Direct ophthalmologic examination.
   - **d.** Auscultation of the lungs and heart.
   - **e.** Evaluation of the abdomen and peripheral pulses for bruits, masses, or deficits.

III. TREATMENT

A. The intensity of intervention is determined by the clinical situation.

B. Goal of initial therapy is to terminate ongoing organ damage, *not* to return BP to normal levels.

C. Goal: 25% reduction from the initial *mean arterial pressure* within the first minutes to hour after initiation of treatment.

D. After initial stabilization, the goal should be reduce BP to 160/100-110 over the next several hours.

1. Patients with acute left ventricular failure, myocardial ischemia, or aortic dissection may require more aggressive treatment to achieve BP < 120/80 mm Hg.
2. Interventions such as intubation, control of seizures, treating withdrawal, hemodynamic monitoring, and maintenance of urine output can be as important as prompt control of BP.
3. Avoid aggressive BP reduction as it may lead to ischemia of the kidneys, brain, or myocardium because of arterial autoregulation. Also, patients with ischemic strokes are often managed with higher than usual BP range.

E. After 24 hours of maintaining BP in the 160/100 range, further BP therapy can be initiated to begin to achieve the final goal BP.

F. Transition from parenteral to oral: In the intensive care unit, parenteral therapy with rapid-acting agents with close hemodynamic monitoring is preferred as it is the most rapid and reliable method to reduce the BP. Once BP is controlled, oral therapy can be initiated and parenteral therapy slowly decreased.

G. Volume status: Many patients without heart failure but with hypertensive emergencies are intravascularly deplete and may require significant volume repletion to maintain organ perfusion while controlling BP.

IV. SPECIAL SCENARIOS OF HYPERTENSIVE EMERGENCIES

A. New onset of severe hypertension in patients without a prior history.

1. Secondary causes, such as pain, anxiety, new onset of angina, hypercarbia or hypoxia, hypothermia, rigors, excessive arousal after sedation, withdrawal, or fluid mobilization with volume overload, can all lead to short-term elevations in BP.
2. If antihypertensive agents are necessary, low doses of short-acting agents should be used to avoid sharp drops in BP in this usually self-limited situation.

B. Perioperative hypertension.

1. *Preoperative*: Moderate chronic hypertension is not a major risk factor for surgery, but it is a marker for potential coronary artery disease.
2. *Perioperative*: BP higher than 160/100 mm Hg or an increase of more than 30 mm Hg (systolic or diastolic) above preoperative is worrisome.
3. *Postoperative*: BPs can vary widely due to an increase in pressor reflexes and central nervous system activity due to pain, hypothermia with shivering, hypercarbia and hypoxia, volume resuscitation, or reflex excitement after anesthesia.

V. PHARMACOLOGIC AGENTS (Table 30-3).

A. Direct vasodilators.

1. *Sodium nitroprusside: the most predictable and effective. It dilates both arterioles and venules (reducing both afterload and preload) and lowers myocardial oxygen demand.*
2. Nitroglycerin: predominantly dilates the venous system.
3. Hydralazine: a direct parenteral arterial vasodilator that will increase cardiac output but may cause a reflex heart rate increase.

B. β-Blockers.

1. Parenteral agents include nonselective and selective agents.
   a. *Labetalol, which has both beta- and alpha-blocking properties, is particularly useful for hypertensive emergencies with immediate BP control with intravenous bolus administration followed by a continuous infusion for maintenance.*
   b. Esmolol is a short-acting, beta-1 selective agent.

C. Calcium antagonists.

1. Dihydropyridines: principally direct vasodilatory effects.
   a. Parenteral.
      i. Nicardipine: a rapid-acting systemic and coronary artery vasodilator with minimal effects on cardiac conductivity or inotropy.
      ii. Nimodipine: recommended only for patients with subarachnoid hemorrhage.
      iii. Clevidipine: parenteral, rapid-onset, and short-acting calcium antagonist that is a potent arterial dilator with little effect on venous capacitance or myocardial contraction.

D. Angiotensin-converting enzyme inhibitors.

1. Captopril: rapid onset of effect after oral administration (30 minutes) with little change in cardiac output or reflex tachycardia.
2. Enalaprilat: the only parenteral angiotensin-converting enzyme inhibitor. Use with caution because of reflex tachycardia. Avoid in acute myocardial infarction (MI).

E. Miscellaneous.

1. Fenoldopam: a parenteral peripheral dopamine type 1 agonist that can be useful in most hypertensive emergencies.

F. Diuretics are not considered primary agents because many patients with hypertensive crises are in fact hypovolemic. In patients who are volume overloaded, loop diuretics, such as furosemide or bumetanide, can help control intravascular volume and maintain urine output.

TABLE 30-3 Proper Dosing for Agents to Treat Hypertensive Crisis

Agent	Administration	Onset	Duration	Special indications
Direct vasodilators				
Nitroprusside	IV infusion: 0.25–10.0 μg/kg/min	Immediate	1–2 min	Most HTN emergencies
Nitroglycerin	IV infusion: 5–200 μg/min	2–5 min	5–10 min	Heart failure or cardiac ischemia
Fenoldopam	IV infusion: 0.1 μg/kg/min Uptitrated by 0.05–0.1 μg/kg/min Increments to max 1.6 μg/kg/min	5–15 min	30 min	Most HTN emergencies; avoid in glaucoma
Hydralazine	IV bolus: 10–20 mg	10–20 min	1–4 h	Eclampsia
Adrenergic blockers				
Phentolamine	IV 5–15 mg	1–2 min	10–20 min	Pheochromocytoma, catecholamine surge
Esmolol	IV bolus 250–500 μg/kg IV bolus repeat after 5 min IV infusion 50–100 mg/kg/min/; give new bolus when increase infusion.	5–10 min	10–30 min	Most HTN emergencies
Labetalol	IV bolus: 20–80 mg q10min to a maximal total dose of 300 mg IV infusion: 0.5–2 mg/min	5–10 min	3–6 h	Most HTN emergencies; not in decompensated heart failure

(continued)

TABLE 30-3 Proper Dosing for Agents to Treat Hypertensive Crisis (*Continued*)

Agent	Administration	Onset	Duration	Special indications
Calcium antagonists				
Nicardipine	IV infusion: 5–15 mg/h	5–10 min	1–2 h	Most HTN emergencies; not in heart failure
Nimodipine	IV infusion: no longer available PO 60 mg q4h	1.5 h	8–9 h	Subarachnoid hemorrhage
Clevidipine	IV infusion: 1–2 mg/h, double dose q90sec. As approach goal BP, ↑ by less than double and lengthen uptitration to q5-10min. Typical goal is 4–6 mg/h.	2–4 min	5–15 min	Most HTN emergencies
Angiotensin-converting enzyme inhibitors				
Captopril	PO 6.25–25 mg; repeat q30 min, if necessary.	1 h	1–4 h	
Enalaprilat	IV bolus: 0.625–5.0 mg (over 5 min) q6h	15–30 min	6–8 h	Acute left ventricular failure; not in MI

IV, intravenous; PO, oral.

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31 Syncope

Adam S. Fein and Karen E. Thomas

I. GENERAL PRINCIPLES

A. Definition: sudden, transient loss of consciousness (TLOC) with loss of postural tone.

II. PATHOPHYSIOLOGY

A. Caused by transient hypoxia and/or hypoperfusion of the cerebral cortices and reticular activating system due to low peripheral resistance and/or low cardiac output.

B. Systolic blood pressure <70 mm Hg or interruption of cerebral blood flow for 8 to 10 seconds usually results in syncope.

C. Pathophysiologic mechanisms potentiating syncopal events are commonly divided into (a) reflex (neutrally mediated) with both vasodepressor and cardioinhibitory effects, (b) orthostatic hypotension with low peripheral resistance and poor venous return, and (c) cardiac causes with insufficient cardiac output.

D. Syncope is one of numerous causes of TLOC. Epileptic seizures, which cause loss of consciousness (LOC) through global interruption of cerebral electrical activity without necessarily impairing blood flow, are another. See Tables 31-1A and 31-1B for causes of LOC.

III. ETIOLOGY

A. Differential diagnosis.

1. The causes of syncope can be classified by etiology and pathophysiology. Please see Table 31-1A.
2. Neurocardiogenic syncope and orthostatic intolerance are most common. Neurologic, cardiovascular, and psychogenic pseudosyncope causes occur with decreasing frequency.
3. Up to 41% of patients will have "syncope of unknown cause" despite a thorough evaluation.
4. Prognosis is related to the severity of underlying disease, with mortality worse in patients with structural cardiac disease. Syncope of cardiac etiology, in the absence of implantable defibrillator, has 1-year mortality of 20% to 30% compared to 0% to 12% for patients with noncardiovascular causes of syncope and 6% for those with syncope of unknown etiology.
5. Younger patients more frequently have syncope due to noncardiovascular cause or syncope of unknown origin and overall have a more favorable prognosis. Older patients more often have a cardiac etiology or syncope due to polypharmacy.

IV. DIAGNOSIS

A. Initial diagnostic evaluation.

1. Goal is to differentiate between benign and potentially life-threatening causes.
2. Presence of cardiovascular disease identifies patients at increased risk of sudden death.

TABLE 31-1A Causes of Syncope

Cardiovascular
- **Arrhythmia**
  - Bradyarrhythmia
    - Sinus node disease
    - AV node disease
    - Drug induced
    - Pacemaker malfunction
  - Tachyarrhythmia
    - Supraventricular arrhythmias
    - Ventricular arrhythmias
- **Low cardiac output**
  - Obstruction to flow
    - Aortic stenosis
    - Mitral stenosis
    - Tricuspid stenosis
    - Hypertrophic cardiomyopathy
    - Atrial myxoma
    - Pulmonary stenosis
    - Pulmonary embolism
    - Pulmonary hypertension
  - Cardiac tamponade
  - Aortic dissection
  - Pump failure (cardiomyopathy, myocardial infarction)

Disorders of autonomic control
- **Autonomic insufficiency**
  - Diabetes mellitus
  - Parkinson disease
  - Primary
- **Reflex mediated**
  - Neurocardiogenic (vasovagal/vasodepressor)
  - Carotid sinus hypersensitivity
  - Situational (cough, defecation, micturition, swallow, postexercise)
  - Neuralgia (trigeminal, glossopharyngeal)

Orthostatic hypotension
- Volume depletion
- Medication related

TABLE 31-1B Causes of Non-syncopal Attacks (Often Confused with Syncope)

Neurologic Event
- Cerebrovascular disease (cerebrovascular accident, TIA)
- Seizure
- Hyperventilation with hypocapnia
- Migraine
- Narcolepsy
- Subclavian steal

Psychiatric illness
- Anxiety or panic disorder
- Major depression
- Somatization
- Munchausen
- Substance abuse

Metabolic
- Hypoadrenalism
- Hypoglycemia
- Hypothyroidism
- Hypoxia

3. History and physical examination alone can identify the etiology of syncope in 45% of patients and suggest a diagnosis in another 40%.

B. History.

1. Ask specifically about situational or provocative factors, postural or exertional symptoms, and prodromal symptoms of cardiac or neurologic origin.
   a. Tongue biting, aching muscles, or disorientation following may suggest a seizure.
   b. Rapid onset of symptoms with a short duration of LOC with loss of postural tone and complete rapid recovery without sequelae are more indicative of cardiac etiology.
   c. Sweating, nausea, vertigo, incontinence, injury, headache, family history of epilepsy, and history of prior concussion are not predictive of seizures.
2. Take a careful medication history.
3. Past medical history should focus on prior syncopal events and cardiac and neurologic history.
4. Family history for cardiomyopathy, sudden cardiac death, or syncope should be sought.

C. Physical examination.

1. Should focus on identifying potential clues as to the etiology of the syncopal episode.
   a. Murmurs, bruits, and signs of heart failure might suggest cardiovascular etiology. In certain situations, provocative maneuvers such as

Valsalva, passive leg raise, and hand grip may be needed to auscultate particular structural heart abnormalities.

b. Neurologic abnormalities such as diplopia, headache, or other focal signs may suggest a neurologic etiology.

2. Orthostatic blood pressure measurements should be taken. However, orthostatic hypotension as etiology of syncope should only be diagnosed when the history and exam are consistent and other etiologies of syncope have been excluded.

D. 12-lead electrocardiogram (ECG).

1. Half the patients presenting with syncope have significant baseline ECG abnormalities. However, the ECG alone is diagnostic of the cause of syncope in fewer than 10% of cases.

2. An abnormal ECG that suggests the presence of underlying heart disease warrants further cardiac evaluation.

3. Some ECG features that may suggest arrhythmia-related syncope include sinus bradycardia or pauses >3 seconds with sinus arrest or sinus node exit block, Mobitz II or third-degree heart block, bifascicular block, alternating left bundle branch block/right bundle branch block (LBBB/RBBB), preexcited QRS complexes, long or short QT intervals, pathologic Q waves, ventricular tachycardia (VT), paroxysmal supraventricular tachycardia, and pacemaker malfunction.

4. The ECG is the principle way to diagnose some genetic disorders that can cause syncope including long QT syndrome and Brugada syndrome (flecainide-induced ST elevation or a saddleback pattern).

E. Laboratory tests.

1. The ordering of blood chemistries, hematologic studies, and cardiac biomarkers such as troponin and brain natriuretic peptide should not be routinely performed but should be guided by the history and physical examination.

F. Cardiac evaluation (Table 31-2).

1. Echocardiography.

a. Part of the initial evaluation for patients with known or suspected cardiac disease.

b. Unselected patients have unanticipated findings 5% to 10% of the time.

c. A finding of structural cardiac abnormalities does not necessarily define a cardiac cause of syncope.

2. Exercise tolerance test (ETT).

a. Should be part of the initial evaluation of patients with syncope during or shortly following exercise with suspected global ischemia or exercise-induced arrhythmias.

b. Rarely reveals the cause of syncope; fewer than 1% have an arrhythmia during ETT.

3. Telemetry/24-hour Holter monitoring.

a. Diagnostic in up to 20% of selected patients with a high possibility of a repeat syncopal event during short-term monitoring (symptoms during monitoring either with or without arrhythmia).

TABLE 31-2 Indications for Cardiac Tests in Patients with Syncope

ECG
All patients at initial presentation

Echocardiogram
Patients with known or suspected cardiac disease (including patients with chest pain, heart murmur, and abnormal ECG)

Exercise tolerance test
Patients with chest pain, ischemic changes on ECG, or exercise-induced or postexertional syncope (who do not undergo cardiac catheterization)

Holter or inpatient ECG telemetry
Patients with symptoms suggestive of arrhythmic syncope (brief LOC, no prodrome, presence of palpitations), unexplained cause of syncope, underlying heart disease, or an abnormal ECG

EP studies
Patients with known or suspected structural heart disease and unexplained syncope or patients with no organic heart disease but recurrent syncope and a negative tilt table test

Tilt table test
Patients with recurrent syncope or patients with a single episode of syncope accompanied by physical injury, motor vehicle accident, or high-risk setting (pilot, surgeon, window washer, etc.) thought to be vasovagal. Indicated in patients with unexplained syncope after other appropriate workup

   b. Longer-term (e.g., 30-day) monitoring using an external event recorder may enhance diagnostic yield for patients with recurring symptoms and a short intersymptom interval.
   c. The majority of patients have no symptoms and no diagnostic arrhythmia during monitoring. Only diagnostic in 1% to 3% of nonselected patients.

4. Electrophysiology study.
   a. Well established for detecting ventricular and supraventricular arrhythmias; less sensitive for detecting bradyarrhythmias.
   b. Diagnostic yield is approximately 30% to 50% in patients with syncope.
   c. A "positive" EP study predicts an increased 3-year sudden death and total mortality rate compared to patients with negative EP studies.
   d. EP studies are low yield in patients without structural heart disease; patients with normal hearts and normal ECGs rarely require electrophysiology testing.

5. Implantable loop recorder.
   a. May be useful for patients with infrequent but recurrent episodes of syncope, with a suspicion of arrhythmogenic cause in the absence of other high-risk clinical features.

b. Can diagnose arrhythmic causes of syncope (frequently bradycardia) in up to 50% of patients, with a superior diagnostic yield compared to traditional provocative lab testing.

c. Prolonged monitoring provides reliable evidence of syncope mechanism, but such a strategy can delay diagnosis and therapy.

G. Evaluation for disorders of autonomic control/reflex-mediated syncope.

1. A number of syncope syndromes are related to abnormal control of autonomic function (Table 31-1). Over 50% of patients with syncope of undetermined etiology may have neurally mediated syncope.

2. Tilt table test.

a. May be used to support the diagnosis of neurocardiogenic (also known as vasodepressor or vasovagal) syncope.

3. Carotid sinus massage.

a. Performed by firm massage of the carotid artery for 5 to 10 seconds in an attempt to elicit a baroreflex-mediated vagal response of bradycardia and/or hypotension.

b. Avoid in patients with recent transient ischemic attack (TIA)/stroke and in those with carotid bruits (reasonable to proceed if Doppler studies exclude significant carotid stenosis).

H. Neurologic evaluation.

1. Patients with focal neurologic signs or symptoms should undergo further evaluation, but this is rarely indicated in the absence of specific clinical abnormalities or suspicion.

2. Head computed tomography (CT).

a. Yields a positive finding in fewer than 5% of patients with syncope.

b. Should be reserved for patients with neurologic abnormality or head trauma.

V. TREATMENT

A. Admission criteria.

1. Hospital admission is suggested for patients with syncope who have.

a. Severe structural or coronary artery disease (heart failure, low ejection fraction, or previous myocardial infarction).

b. ECG features suggesting arrhythmic syncope (nonsustained VT, bifascicular block, inadequate sinus bradycardia (<50 beats/min) or sinoatrial block, preexcited QRS complex, increased QT interval, ECG findings suggesting an inherited disease).

c. Clinical features suggesting arrhythmic syncope (syncope during exertion or supine position, palpitations or chest pain at the time of syncope, associated injury, family history of sudden cardiac death).

d. Important comorbidities: severe anemia, electrolyte disturbance, or frequent syncope.

e. Moderate to severe orthostatic hypotension.

2. Intensive care unit (ICU) admission should be strongly considered in syncope patients with

a. Sustained VT or symptomatic nonsustained VT.

b. Second- or third-degree heart block.

c. Symptomatic bradycardia or pauses >3 seconds.
d. Severe aortic stenosis or severe CHF.
e. Evidence of acute ischemia.
f. Ongoing hemodynamic instability.

VI. SPECFIC TREATMENTS

A. Arrhythmias: Guidelines for implantation of permanent pacemakers and ICDs for patients with syncope are summarized in Table 31-3.

B. Neurally mediated syndromes.

1. Patients should be counseled to avoid potential triggers and to sit or lie down and/or perform isometric contractions at the onset of prodromal symptoms.

TABLE 31-3 Current ACC/AHA Guidelines for Implantation of Permanent Pacemakers and Implantable Cardioverter–Defibrillators in Patients with Syncope

Indication for implantation of pacemakers in patients with syncope

- Symptomatic sinus pauses or sinus bradycardia (Class I)
- Bradycardia and second- or third-degree AV block (Class I)
- Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of >3 sec duration in the absence of any medication that depresses sinus node or AV conduction (Class I).
- Recurrent syncope without clear provocative events and with a hypersensitive cardioinhibitory response (Class IIa)
- Major abnormalities of sinus node function or AV conduction discovered or provoked at electrophysiology study (Class IIa)
- Chronic bifascicular or trifascicular block and syncope not proved to be due to AV block when other likely causes have been excluded, specifically VT (Class IIa)
- Neurally mediated syncope with significant bradycardia reproduced by a head-up tilt (Class IIb)

Indication for implantation of ICD in patients with syncope

- Clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiology study (Class I)
- Significant left ventricular dysfunction, nonischemic dilated cardiomyopathy, and unexplained syncope (Class IIa)
- Patients with long QT syndrome or catecholaminergic polymorphic VT with recurrent syncope on beta-blocker therapy (Class IIa)
- Patients with Brugada syndrome (Class IIa)
- Advanced structural heart disease and unexplained syncope despite noninvasive and invasive evaluation (Class IIb)

Class I: evidence and/or general agreement that treatment is beneficial.
Class IIa: conflicting evidence and/or divergence of opinion but weight of evidence/opinion is in favor of treatment.
Class IIb: conflicting evidence and/or divergence of opinion with treatment efficacy less well established.

2. In patients with orthostatic intolerance, the primary treatment is hydration (2 to 3 L/day) and salt repletion (approximately 10 g NaCl/day).
3. Beta-adrenergic blockers, selective serotonin reuptake inhibitors (e.g., fluoxetine), and alpha-adrenergic agonists (midodrine) have demonstrated mixed efficacy in randomized trials on the treatment of reflex syncope. Midodrine and fludrocortisone have been shown to benefit patients with autonomic failure.
4. Patients with recurrent, medically refractory vasovagal syncope associated with marked bradycardia may benefit from implantation of a permanent pacemaker.
5. Consider pacemaker implantation in patients with severe bradycardic response to carotid sinus massage after other potential causes of syncope are excluded.

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Guidelines for indications of pacemaker and ICD implantation.

32 Management of Unstable Angina and Non–ST Elevation Myocardial Infarction

Yuri B. Pride and Eli V. Gelfand

I. GENERAL PRINCIPLES AND DEFINITIONS

A. More than 6 million patients present to the emergency department with chest pain annually in the United States.

B. More than 1.1 million patients are admitted to the hospital each year in the United States with an acute coronary syndrome (ACS).

C. Eighty percent of ACS patients do not have ST-segment elevations on an initial ECG and have unstable angina or non–ST-segment elevation myocardial infarction (UA/NSTEMI).

II. PATHOPHYSIOLOGY

A. UA/NSTEMI is caused by either rupture of a vulnerable atherosclerotic plaque or erosion of endothelium revealing underlying atherosclerotic debris followed by the formation of thrombus.

B. In contrast to ST-segment elevation MI (STEMI), in UA/NSTEMI, the intracoronary thrombus is typically only partially occlusive, although intermittent periods of occlusion and subsequent reperfusion are common.

C. There is embolization of the thrombus fragments downstream, causing additional myocardial ischemia and necrosis.

D. The sequence of events in UA/NSTEMI is

1. Rupture or erosion of a vulnerable atherosclerotic plaque.
2. Platelet activation, aggregation, and adhesion.
3. Secondary activation of plasma coagulation cascade.
4. Coronary vasoconstriction.
5. Imbalance in myocardial oxygen and demand.
6. Downstream embolization of platelet microaggregates, thrombus, and atherosclerotic debris.

III. GENERAL ASPECTS OF DIAGNOSIS

A. Based on new or accelerating symptoms of coronary ischemia, with or without ECG changes.

B. Elevation of cardiac troponin beyond 99th percentile of normal distinguishes NSTEMI from UA.

C. ECG changes in UA/NSTEMI may include:

1. ST-segment depressions.
2. Transient ST-segment elevations.
3. New T-wave inversions.

IV. INITIAL EVALUATION AND RISK STRATIFICATION OF SUSPECTED UA/NSTEMI

A. Focused **history** should concentrate on the nature of anginal symptoms, prior history of coronary artery disease (CAD), and traditional cardiovascular risk factors.

B. **Physical examination** is directed toward assessment of

1. Possible precipitants of UA/NSTEMI, such as hypertension, thyroid disease, anemia, or arrhythmias.
2. Hemodynamic effects of UA/NSTEMI, such as congestive heart failure and arrhythmia.
3. Important alternate diagnoses; for example, acute pericarditis, pulmonary embolism, or aortic dissection.

C. **12-lead ECG** should be interpreted within 10 minutes of the patient's arrival to the emergency department.

1. If initial ECG is not diagnostic of ACS, follow-up ECG should be performed every 15 to 30 minutes to evaluate for evolving ST-segment elevations or depressions.
2. Posterior leads V_7-V_9 should be utilized to enhance detection of posterior MI if there are ST-segment depressions in the anterior precordial leads (V_1-V_3).

D. Cardiac biomarkers, preferably **cardiac-specific troponin,** should be measured.

1. For patients presenting within 6 hours of symptom onset, considerations are to
   a. Measure myoglobin (a very early marker of myocardial necrosis) along with troponin.
   b. Repeat troponin levels in 6 to 8 hours or as guided by timing of symptom onset.
2. Additional biomarkers, such as total CK-MB mass, B-type natriuretic peptide (BNP), or N-terminus proBNP (NT-pro-BNP), may have additional prognostic information in UA/NSTEMI.

E. Among patients with new left bundle branch block or a concerning history without diagnostic ECG changes, consideration should be given to performing bedside echocardiography to assess for regional wall motion abnormalities.

F. Focused evaluation for **other causes of chest discomfort** should be undertaken (Table 32-1).

G. Based on the clinical history, ECG and initial laboratory, and imaging tests, patients are assigned the probability of having ACS. Further triage and management decisions are made accordingly.

1. In patients with **noncardiac chest pain**, a search is undertaken in the ED for the underlying cause.

TABLE 32-1 Differential Diagnosis of Chest Discomfort

Conditions with immediate life-threatening potential
- ACS
- Acute aortic dissection
- Pulmonary embolism/infarction
- Esophageal rupture
- Tension pneumothorax

Other common conditions
- Acute pericarditis
- Gastroesophageal reflux disease
- Costochondritis and related musculoskeletal conditions
- Acute myocarditis
- Transient apical ballooning syndrome ("takotsubo-type" cardiomyopathy)
- Esophageal spasm
- Pleurisy
- Referred pain from abdominal organs, particularly the spleen and gallbladder

2. Patients with **stable angina** benefit from uptitration of antianginal therapy with or without observation in a dedicated chest pain unit.
3. Patients with **possible UA/NSTEMI** who have a nondiagnostic ECG and normal initial cardiac biomarkers are observed for at least 6 to 12 hours from symptom onset.
   a. If recurrent ischemic pain or follow-up studies are positive, treatment for definite ACS is initiated.
   b. If there is no further pain and ECG/biomarkers remain within the range of normal, a stress test should be considered.
      i. If stress test demonstrates inducible ischemia or new regional left ventricular (LV) systolic dysfunction, therapy for ACS is started.
      ii. If stress test is negative, a diagnosis of noncardiac chest pain is likely and arrangements should be made for outpatient follow-up.
4. Among patients with a nondiagnostic ECG and negative cardiac biomarkers, coronary computed tomography (CT) can also be considered. It has a high negative predictive value, and it may help determine patients who are safe for discharge from the emergency department.
5. Patients with probable/definite UA/NSTEMI are admitted to a coronary care or telemetry unit for continuous cardiac monitoring, risk stratification, antithrombotic and antianginal therapy, and consideration of revascularization.

H. Patients with UA/NSTEMI must be risk stratified, as certain therapies have been shown to benefit only high-risk patients.

I. **TIMI risk score** (Table 32-2) provides a rapid way of assessing the patient's risk.

1. Has been prospectively validated in UA/NSTEMI.

TABLE 32-2 TIMI Risk Score for UA/NSTEMI

Age ≥65 y	1 pt
Prior coronary stenoses >50%	1 pt
≥3 Risk factors for CAD	1 pt
Use of aspirin in the preceding 24 h	1 pt
≥2 Anginal events in the preceding 24 h	1 pt
ST-segment changes	1 pt
Elevated cardiac biomarkers	1 pt
Total possible score	**0–7 pts**

Adapted from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284(7):835–842.

2. Useful in predicting short-term (14 to 30 days) major adverse cardiovascular events (death, MI, or recurrent ischemia) and long-term (1-year) mortality.
3. Higher-risk score identifies patients who progressively benefit from aggressive therapy with low molecular weight heparin (LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and early invasive strategy.

V. MANAGEMENT OF UA/NSTEMI

A. General aspects of care.

1. Dual goals in management of UA/NSTEMI must be taken into account at all times.
   a. Immediate **relief of myocardial ischemia.**
   b. **Prevention of adverse outcomes**, specifically [re]infarction, death, and future heart failure.
2. The overall management plan is described in Figure 32-1.
3. The general plan of management of patients with UA/NSTEMI should develop as follows.
   a. Establish **basic care and monitoring**: oxygen, continuous ECG monitoring, and resuscitation equipment.
   b. Administer **analgesic and anti-ischemic therapy**: beta-blockers, nitrates, and morphine.
   c. **Define risk** using a standardized scoring system (see above).
   d. Determine the appropriate overall treatment strategy.
      i. **Early invasive strategy:** planned cardiac catheterization within 4 to 48 hours with revascularization where feasible.
      ii. **Conservative strategy:** medical management with revascularization dictated by recurrent ischemia at rest or upon provocative testing.

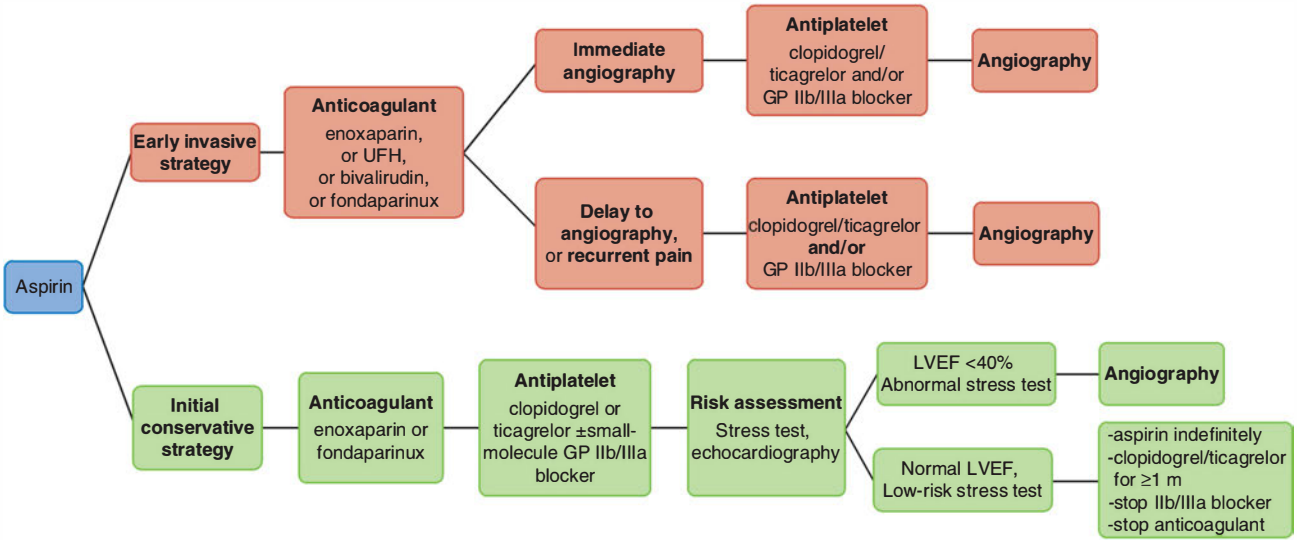

Figure 32-1. Overall contemporary treatment strategy for UA/NSTEMI. (Data from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 2007;50(7):e1–e157.)

e. Administer **antithrombotic therapy**, according to risk and planned strategy.
   i. *Antiplatelet therapy:* aspirin, clopidogrel, prasugrel, ticagrelor, and/or GPIIb/IIIa inhibitors.
   ii. *Anticoagulant therapy*: unfractionated heparin (UFH), LMWH, bivalirudin, or fondaparinux.

B. Anti-ischemic, analgesic, and other initial therapy.

1. **Nitrate** therapy is recommended initially, with the use of sublingual or intravenous nitrates for ongoing ischemic pain. Nitrates can be safely discontinued upon successful revascularization.
2. **Beta-blockade** remains a cornerstone of treatment of ACS and should be administered to patients, targeted to a heart rate of 50 to 60 bpm, in the absence of the following contraindications.
   a. Signs of decompensated heart failure or low-output state.
   b. Second- or third-degree heart block.
   c. Active bronchospasm.
3. **Morphine sulfate** is very effective in treating anginal discomfort and also modestly reduces heart rate and blood pressure. It should be used with careful monitoring, when nitrates and beta-blockers are not successful in completely relieving the chest pain.
4. **Angiotensin-converting enzyme (ACE) inhibitors** are indicated within the first 24 hours in patients with pulmonary congestion or LV ejection fraction <40% and have shown benefits in reducing the rate of death and recurrent hospitalization in these patients. Angiotensin receptor blockers (ARBs) may be used in place of ACE inhibitors in patients with known intolerance to ACEi, but combined use of ACEi and ARBs is not recommended.

TABLE 32-3 Comparison of Early Invasive and Conservative Strategies for UA/NSTEMI

Early invasive	Conservative
Advantages	
• Identifies patients with severe CAD who derive survival benefit from CABG • Identifies patients without significant CAD • PCI and CABG can reduce subsequent hospitalization and complicated antianginal therapy	• Avoids routine early use of invasive procedures • More widely available
Limitations	
• Potential vascular and bleeding complications • Significant upfront costs • Not available in all facilities	• Coronary revascularization not routinely achieved • Patients with "surgical" CAD or without CAD are not identified.

C. Invasive versus conservative strategy.

1. Advantages and disadvantages of each strategy are outlined in Table 32-3.
2. Several large randomized trials systematically compared the two strategies with the following findings.
   a. Intermediate- and high-risk patients (as assessed with standard risk scores) derive a benefit from an **early invasive strategy**. This especially includes patients with
      i. ST-segment changes.
      ii. Elevated cardiac biomarkers.
      iii. History of prior revascularization.
   b. Stable, low-risk patients may be managed initially with a conservative strategy.
3. Patients who may specifically benefit from a conservative strategy include those with
   a. Advanced malignancy and a limited life expectancy, where accumulated benefits of revascularization are not likely to be relevant.
   b. Intracranial pathology that precludes long-term dual antiplatelet therapy or intensive periprocedural anticoagulation.
   c. CAD known to not be amenable to revascularization.

D. Antiplatelet therapy.

1. **Aspirin** reduces recurrent cardiovascular events by up to 50%, as compared with placebo; is effective across a broad range of risk profiles; and should be started immediately in all patients and continued indefinitely. Initial recommended dose of aspirin is 162 to 325 mg PO. Recommended maintenance dose is discussed below.
2. **Clopidogrel, prasugrel, and ticagrelor** block the adenosine diphosphate pathway and decrease platelet activation and aggregation. Clopidogrel has significant variability of antiplatelet activity across patients, while prasugrel and ticagrelor have little variability. Moreover, prasugrel and ticagrelor have more rapid onset of action.
   a. A loading dose followed by a maintenance dose of clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg) should be administered to patients intolerant of or allergic to aspirin.
   b. Because of a higher risk of bleeding, prasugrel is contraindicated among patients >75 years of age, those weighing <60 kg, or those who have a history of stroke or transient ischemic attack.
3. Intravenous GP IIb/IIIa inhibitors prevent fibrin from binding to platelets and thus inhibit platelet aggregation. **Abciximab** is a monoclonal antibody, and **tirofiban** and **eptifibatide** are small-molecule GP IIb/IIIa inhibitors.
4. Dual antiplatelet therapy with aspirin and clopidogrel, ticagrelor, or an intravenous GP IIb/IIIa inhibitor (eptifibatide or tirofiban preferred) should be administered to patients with moderate- to high-risk UA/NSTEMI undergoing an early invasive strategy.
   a. If a second antiplatelet agent is deferred prior to PCI, clopidogrel, prasugrel, ticagrelor, or an intravenous Gp IIb/IIIa inhibitor can be administered at the time of PCI.

b. If an initial conservative strategy is chosen, clopidogrel or ticagrelor should be added to aspirin. An intravenous GP IIb/IIIa inhibitor can be added if there are refractory symptoms.

i. **Dual antiplatelet therapy** increases the risk of bleeding, especially in the setting of cardiac surgery. It is recommended that clopidogrel and ticagrelor be stopped 5 days prior to elective coronary artery bypass grafting (CABG) and prasugrel 7 days prior to elective CABG. **Therefore, some centers** accept a delay in clopidogrel or ticagrelor administration until angiography demonstrates that CABG is *unlikely* to be required, provided that the angiography itself is done expeditiously.

c. A loading dose of 600 mg of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor is recommended among patients undergoing PCI.

5. The maintenance dose of aspirin *and* duration of ADP receptor antagonist therapy both depend on the management of ACS as follows:

a. **Medical management without stent**: aspirin 75 to 162 mg indefinitely *plus* clopidogrel 75 mg/day or ticagrelor 90 mg twice daily for at least 1 month uninterrupted and ideally for 1 year.

b. **Bare metal stent**: aspirin 162 to 325 mg for 1 month, then 75 to 162 mg indefinitely *plus* clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg twice daily for at least 1 month and ideally for 1 year.

c. **Drug-eluting stent**: aspirin 162 to 325 mg for 1 month, then 75 to 162 mg indefinitely *plus* clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg twice daily for at least 1 year uninterrupted.

E. Anticoagulant therapy.

1. It is recommended that all patients with UA/NSTEMI receive an anticoagulant, with one of four choices, as outlined below. If PCI is required, a consistent antithrombotic strategy should be maintained whenever feasible.

a. **Unfractionated heparin** (UFH).

i. Reduces the rate of death or myocardial infarction by 33% versus placebo in a meta-analysis of six trials.

ii. Typically titrated to an activated partial thromboplastin (aPTT) time of 50 to 70 seconds.

iii. Caution must be exercised to avoid excess anticoagulation by careful aPTT monitoring.

iv. Should be continued for 48 hours among patients undergoing an initial conservative strategy who are deemed low risk and until PCI is performed among patients undergoing an early invasive strategy.

b. **Low molecular weight heparin** (LMWH) enoxaparin should be added to the medical regimen for all patients with UA/NSTEMI.

i. Five of the six trials comparing enoxaparin with UFH favored enoxaparin, with lower rates of cardiovascular death or nonfatal MI.

ii. Benefits of enoxaparin over UFH are substantial with conservative strategy and less so with early invasive management.

c. A direct thrombin inhibitor **bivalirudin** may be used in place of a heparin in patients treated with an early invasive strategy.

i. Associated with lower rates of bleeding versus GP IIb/IIIa inhibitor *plus* heparin.

ii. If bivalirudin is chosen over a heparin-based strategy, patients should also be treated with concomitant clopidogrel.

iii. Among patients initially treated with UFH or LMWH, bivalirudin can be administered in the cardiac catheterization laboratory to support PCI.

d. Factor Xa inhibitor **fondaparinux** results in a more sustained and predictable anticoagulation than heparin, is administered once daily subcutaneously, and does not require measurement of levels but does not act against preformed thrombi—especially important during PCI—where intracoronary hardware may be prone to thrombosis.

i. Fondaparinux-based therapy is suggested for conservatively treated patients at a high risk for bleeding.

ii. If patients go on to PCI, use of UFH or bivalirudin for procedural anticoagulation is recommended.

F. *Thrombolysis.*

1. Thrombolytic therapy is not recommended as treatment for UA/NSTEMI.

a. Thrombolytics have been shown to result in worse outcomes in UA/NSTEMI, possibly because they activate platelets, and could also lead to hemorrhage into a nonocclusive plaque with subsequent coronary occlusion.

G. *Strategies for coronary revascularization.*

1. Revascularization is most beneficial when performed in high-risk patients, early in the hospital course.

2. Introduction of drug-eluting stents has reduced the rates of in-stent restenosis. Newer-generation stents likely have no increase in very late stent thrombosis compared with bare metal stents.

a. Dual antiplatelet therapy is required for 1 year following drug-eluting stent implantation and 1 month following bare metal stent implantation.

3. Decision regarding the choice of revascularization technique (PCI vs. CABG) is largely dependent on

a. Coronary anatomy.

b. LV systolic function.

c. Medical comorbidities, for example, diabetes, peripheral vascular disease, stroke, and coagulopathy.

d. Patient's compliance.

i. Especially important when considering placement of a drug-eluting stent, where uninterrupted, long-term, dual antiplatelet therapy is required.

4. A treatment strategy based on the coronary anatomy and medical comorbidities is given in Figure 32-2.

H. Long-term secondary prevention.

1. Patients with UA/NSTEMI are at a high risk for recurrence. Validated risk scores exist to estimate an individual's risk of recurrent vascular events and mortality (Fig. 32-3).

2. Five classes of drugs currently receive a strong recommendation from ACC/AHA for long-term medical therapy.

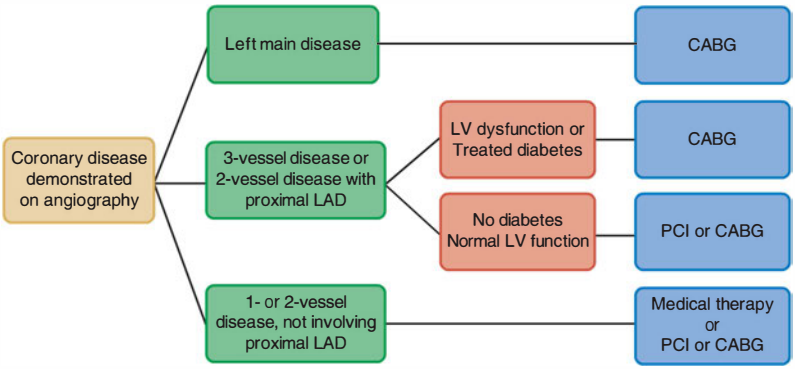

Figure 32-2. Revascularization strategy for UA/NSTEMI. (Adapted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 2007;50(7):e1–e157.)

   a. **Aspirin.**
   b. **Clopidogrel.**
   c. **Beta-blockers.**
   d. **ACE inhibitors.**
   e. **Statins.**

3. For plaque stabilization, statins and ACE inhibitors are recommended in the long term.
   a. High-dose statins should be used primarily, and a target LDL should be <70 mg/dL.
   b. Secondary goal of HDL >40 mg/dL is reasonable.
4. Beta-blockers may help decrease "triggers" for MI during follow-up.
5. Dual antiplatelet therapy is started at the time of the acute event and continued as discussed earlier.
6. Other goals that should be emphasized prior to discharge include:
   a. Complete smoking cessation.
   b. Achievement of ideal body weight.
   c. Regular physical activity.
   d. Glycemic control in diabetic patients.
   e. Eliminating or minimizing the use of nonsteroidal anti-inflammatory drugs and COX-2 inhibitors.
   f. Education on medication adherence, especially dual antiplatelet therapy.

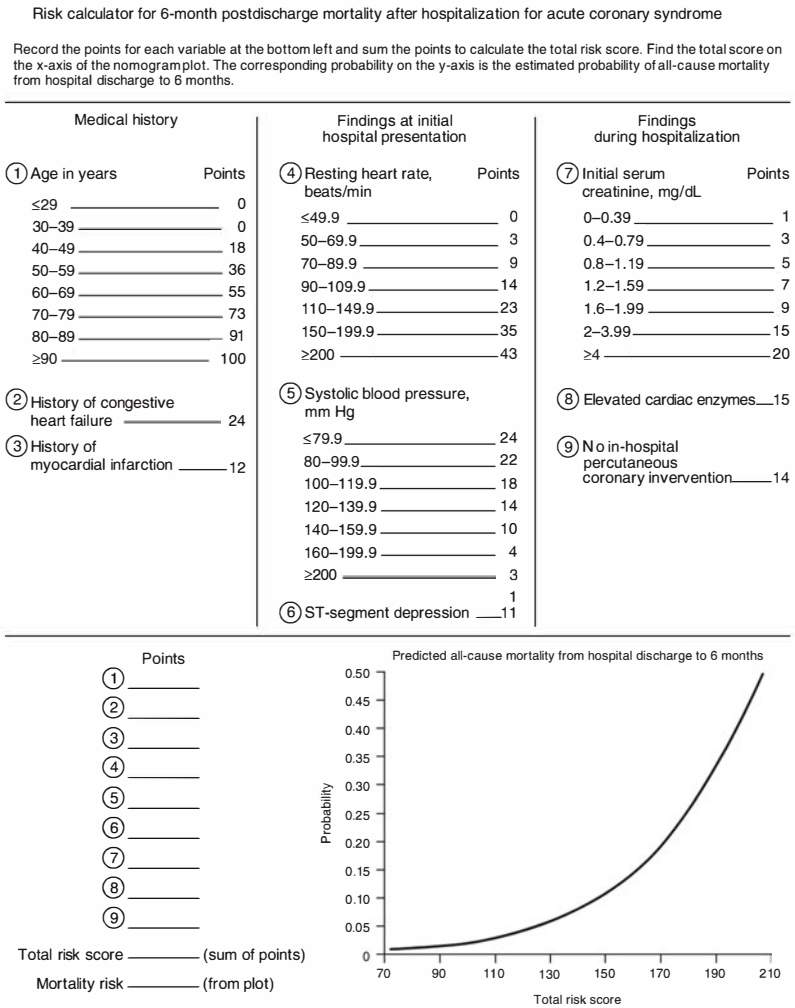

Figure 32-3. GRACE prediction scorecard for all-cause mortality from discharge to 6 months. (Reproduced from Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291(22):2727–2733.)

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33 ST-Segment Elevation Myocardial Infarction

Ian J. Neeland and James A. de Lemos

I. GENERAL PRINCIPLES

A. Rapid reperfusion of the infarct-related artery (IRA), with either primary percutaneous coronary intervention (PCI) or fibrinolytic therapy, is the cornerstone of management for patients with ST-segment elevation myocardial infarction (STEMI).

B. Adjunctive therapy with aspirin, $P2Y_{12}$ receptor inhibitors, β-blockers, angiotensin-converting enzyme inhibitors, and statins further reduces the risk of death and major cardiovascular events after reperfusion.

II. PATHOPHYSIOLOGY

A. Rupture of lipid-rich, inflammatory atherosclerotic plaque causes collagen exposure leading to platelet adhesion, activation, and aggregation.

B. Fibrin–platelet clot develops as thrombin converts fibrinogen to fibrin and completely occludes the IRA causing transmural myocardial injury, manifested by ST-segment elevation on the electrocardiogram (ECG).

III. DIAGNOSIS

A. Differential diagnosis: Rapidly consider/rule out pneumothorax, aortic dissection, pericarditis, tamponade, pulmonary embolism, stress cardiomyopathy with apical ballooning (takotsubo syndrome), and severe hyperkalemia.

B. History.

1. Severe, pressure-type midsternal pain, often with radiation to the left neck, arm, or jaw, occurring at rest.
2. Associated symptoms: dyspnea, nausea, vomiting, diaphoresis, or weakness.
3. Silent infarction in 25% of cases, especially in elderly and diabetic patients.

C. Physical examination.

1. Not helpful in confirming the diagnosis of STEMI.
2. Should focus on eliminating other potential diagnoses and assessing for complications of STEMI (Tables 33-1 and 33-2).

D. ECG.

1. ST elevations in regional vascular distribution with concurrent ST depression in reciprocal leads.

2. ECG mimics: pericarditis (global ST elevation with PR depression), early repolarization, old left ventricular (LV) aneurysm, and Prinzmetal angina.
3. New left bundle branch block (LBBB) may represent large anterior infarction, but has a high false-positive rate; primary PCI strongly preferred over fibrinolytic therapy for LBBB.

E. Cardiac biomarkers.

1. Biomarkers of limited use for emergency diagnosis of STEMI.
2. Cardiac troponins are the preferred biomarkers for confirmation of myocardial infarction (MI).

F. Additional evaluation.

1. Echocardiography useful when ECG is indeterminate to evaluate for focal wall motion abnormalities.
2. Risk assessment scores predict early mortality and recurrent infarction.
   TIMI (http://www.mdcalc.com/timi-risk-score-for-stemi).
   GRACE (http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html).

TABLE 33-1 Electrical Complications of Acute MI

Complication	Prognosis	Treatment
Ventricular tachycardia/fibrillation		
Pulseless arrest at presentation	Variable	Defibrillation; therapeutic hypothermia if comatose
VT/VF within first 24–48 h	Good	Immediate cardioversion; lidocaine; β-blockers
VT/VF > 48 h	Poor	Immediate cardioversion; electrophysiology study/implantable defibrillator; amiodarone
Bradyarrhythmias		
Sinus bradycardia	Excellent	Atropine for hypotension or symptoms
Second-degree heart block		
Mobitz type I (Wenkebach)	Excellent	Atropine for hypotension or symptoms
Mobitz type II	Guarded	Temporary pacemaker
Complete heart block		
Inferior MI	Good	Temporary pacemaker
Anterior MI	Poor	Temporary pacemaker followed by permanent pacemaker
Atrial tachyarrhythmias		
Atrial fibrillation	Good	β-Blocker and/or amiodarone; cardioversion if unstable

VT, ventricular tachycardia; VF, ventricular fibrillation; MI, myocardial infarction.

TABLE 33-2 Mechanical Complications of Acute MI

Complication	Timing	Pathophysiology	Exam/ECG	Intervention
Cardiogenic shock	Early	Extensive LV infarction; mechanical complications (see below)	Tachycardia, hypotension, cool and clammy extremities, altered mentation	Emergent PCI or CABG; IABP[a]; LVAD for refractory cases
Acute MR	Early	Necrosis of papillary muscles that tether mitral valve	Heart failure; early systolic, decrescendo, or holosystolic murmur; thrill radiating to apex ± S3	Emergent echo; right heart catheterization: large V waves. IABP; surgery
LV rupture	Acute—subacute	Necrosis of LV causing free wall rupture and flow into pericardial chamber	Usually presents as sudden death or tamponade; hypotension, muffled heart sounds, elevated JVP	IV fluids, emergent echo; pericardiocentesis[b] emergent surgery
RV MI	Acute	Hypokinesis or akinesis of right ventricle	Hypotension, elevated JVP; congested liver; ST elevations in V1, (±V2, V3), V3R, V4R	IV fluids; temporary pacemaker; emergent catheterization; nitrates contraindicated
LV aneurysm	Late (weeks to months)	Regional dilation and dyskinesis of LV. Risk of thrombus and arrhythmias	ECG shows persistent ST-segment elevation	Echo; oral anticoagulation

[a]IABP may not reduce 30-day mortality in patients with cardiogenic shock for whom an early revascularization strategy is planned.
[b]Pericardiocentesis should be avoided if patient has stable blood pressure, because this may precipitate hemodynamic collapse.
VSD, ventricular septal defect; IABP, intraaortic balloon pump; LVAD, left ventricular assist device; MR, mitral regurgitation; LV, left ventricle; IVF, intravenous fluids; RV, right ventricle; MI, myocardial infarction; LLSB, left lower sternal border; JVP, jugular venous pressure; ECG, electrocardiogram.

IV. REPERFUSION THERAPY

A. Goal is rapid and complete restoration of epicardial and microvascular blood flow using pharmacologic and/or mechanical reperfusion.

1. Reperfusion method depends on the availability of PCI within 120 minutes of first medical contact (Fig. 33-1).
2. Resolution of ST-segment elevation is the best indicator of successful reperfusion.
3. Thrombolysis in myocardial infarction (TIMI)-3 flow within 1 hour decreases mortality by 50%.

B. Guidelines for reperfusion therapy in non-PCI centers.

1. Transfer for primary PCI if access to PCI-capable hospital within 120 minutes of first medical contact or if patient has contraindication to fibrinolysis (Table 33-3).
2. If primary PCI not available within 120 minutes, administer fibrinolytics within 30 minutes of arrival if symptom onset ≤12 hours and no contraindications (Table 33-4).
3. Fibrinolytic therapy not indicated if symptoms >24 hours or for non-STEMI.
4. Primary PCI preferred if patient is in cardiogenic shock.

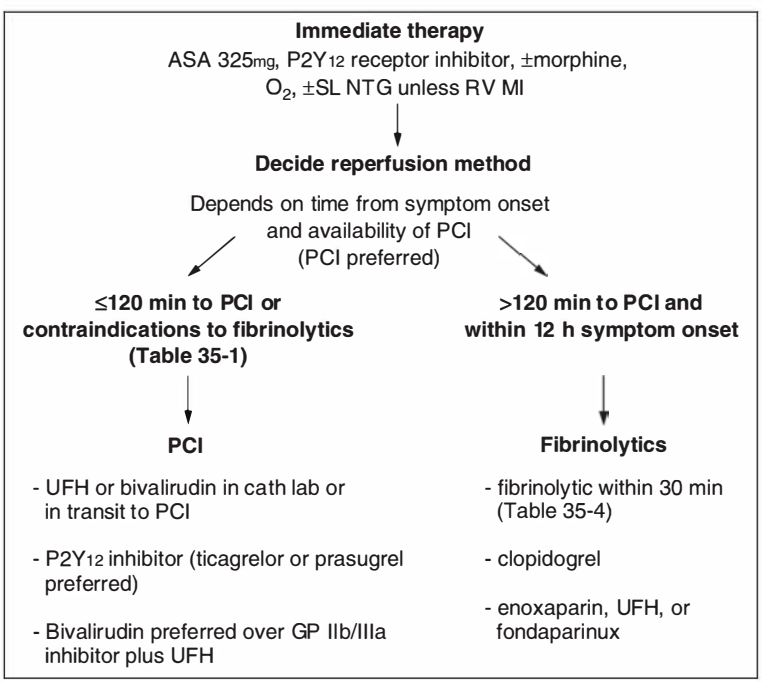

Figure 33-1. Immediate therapy overview. ASA, aspirin; O_2, oxygen; SL NTG, sublingual nitroglycerin; RV MI, right ventricular myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; GP, glycoprotein.

TABLE 33-3 Contraindications to Fibrinolytic Therapy

Absolute contraindications	Relative contraindications
Active internal bleeding	Blood pressure >180/110 mm Hg
Any history of CNS hemorrhage	History of ischemic stroke, dementia, AVM >3 mo
Ischemic stroke within 3 mo	Recent (2–4 wk) internal bleeding
Significant head trauma within 3 mo	Prolonged CPR (>10 min)
Known cerebrovascular lesion (e.g., AVM)	Oral anticoagulant therapy
CNS neoplasm	Pregnancy
Suspected aortic dissection	Major surgery or trauma within 3 wk
Intracranial or intraspinal surgery within 2 mo	Active peptic ulcer
Severe hypertension unresponsive to initial treatment	Puncture of a noncompressible vessel

CNS, central nervous system; AVM, arteriovenous malformation; CPR, cardiopulmonary resuscitation.

TABLE 33-4 Comparison of Fibrinolytic Therapies

	Alteplase (tPA)	Tenecteplase (TNK-tPA)	Reteplase (rPA)	Streptokinase (SK)
Fibrin selective	+++	++++	++	–
Half-life	5 min	17 min	14 min	20 min
Dose	15-mg bolus; then 0.75 mg/kg over 30 min; then 0.5 mg/kg over 60 min	0.53 mg/kg as a single-dose bolus	Two 10-unit bolus doses given 30 min apart	1.5 million units over 30–60 min
Weight adjusted	Partial	Yes	No	No
Possible allergy	No	No	No	Yes
Efficacy vs. tPA	NA	Equivalent	Similar	1% ↑ Mortality
Safety vs. tPA	NA	Similar ICH ↓ Non-ICH bleeding	Similar	↓ ICH ↓ Overall bleeding
Cost	+++	+++	+++	+

ICH, intracranial hemorrhage; tPA, tissue plasminogen activator (alteplase); NA, not available; the pluses and minuses represent the relative degree of fibrin selectivity or relative expense of the medication.

C. Limitations to fibrinolytic therapy.

1. Intracranial hemorrhage in approximately 1%; higher in elderly, women, low body weight, and uncontrolled hypertension.
2. TIMI-3 flow is achieved in only 50% to 60% of patients. PCI achieves TIMI-3 flow in 80% to 90% of cases.

D. PCI after fibrinolysis.

1. *Elective* PCI indicated 3 to 24 hours after successful fibrinolysis to reduce recurrent MI.
2. *Emergent* (i.e., rescue) PCI only indicated following fibrinolysis for patients with failed fibrinolysis (<50% ST-segment resolution, ongoing chest pain, rising cardiac biomarkers), cardiogenic shock, heart failure, or anterior infarction.

E. Primary PCI.

1. Reduces mortality, increases TIMI-3 flow, decreases stroke risk (including ICH), and decreases reocclusion and recurrent MI when compared with fibrinolytics.
2. Intracoronary stenting decreases reocclusion and restenosis when compared with balloon angioplasty alone.
   a. Drug-eluting stent (DES) preferred over bare metal stent (BMS) due to less restenosis and recurrent ischemia/revascularization.
   b. DES requires ASA and $P2Y_{12}$ inhibitor consistently for 12 months. Consider medical compliance, bleeding risk, and future surgeries. If in doubt, choose BMS.

V. ADJUNCTIVE ANTITHROMBOTIC THERAPY

A. Antiplatelets: aspirin (ASA) and $P2Y_{12}$ inhibitors.

1. ASA reduces mortality, reocclusion, and reinfarction.
2. Administer ASA 162 to 325 mg chewed at presentation; continue daily at 81 mg indefinitely. Higher ASA dosages no longer indicated even with DES.
3. $P2Y_{12}$ inhibitor indicated in all STEMI patients for 1 year regardless of reperfusion method.
   a. Clopidogrel, prasugrel, or ticagrelor indicated for STEMI patients who receive a stent. Prasugrel and ticagrelor may be preferred over clopidogrel if bleeding risk is low but should be avoided in patients on ASA and warfarin (triple therapy).
   b. Prasugrel contraindicated if prior stroke or transient ischemic attack.
   c. Clopidogrel is the only agent indicated for patients treated with fibrinolysis alone.

B. Parenteral anticoagulants.

1. Primary PCI.
   a. Bivalirudin monotherapy associated with lower bleeding rates than UFH plus GP IIb/IIIa inhibitor.
   b. UFH titrated to ACT level in cath lab, with or without GP IIb/IIIa inhibitor.

2. Fibrinolytic therapy.
   a. UFH administered IV 60 units/kg bolus, then 12 units/kg/h.
   b. Enoxaparin 30-mg bolus IV + 1 mg/kg SQ every 12 hours. For patients ≥75 years omit bolus and reduce dose to 0.75 mg/kg every 12 hours.
   c. Fondaparinux 2.5 mg IV initial dose, then SQ every 24 hours.

C. Warfarin indicated for LV thrombus, mechanical heart valve, atrial fibrillation; caution regarding triple therapy with ASA, clopidogrel, and warfarin due to bleeding risk.

VI. ANTIISCHEMIC THERAPY

A. β-Blockers (BB).

1. Limit size of infarction, decrease recurrent MI, improve survival, and prevent arrhythmias and cardiac rupture.
2. Administer BB orally within 24 hours only if hemodynamically stable without heart failure, AV block, or active asthma.
3. IV BB increase cardiogenic shock and are rarely indicated except for control of hypertension, arrhythmias, and ongoing ischemia.
4. Once the patient is hemodynamically stable, continue oral BB for at least 3 years.

B. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB).

1. Prevent heart failure and death by halting adverse remodeling of LV chamber.
2. Indicated within 24 hours with anterior MI, low left ventricular ejection fraction (LVEF) (≤40%), or heart failure.
3. ARBs for patients who cannot tolerate ACEI.

C. Aldosterone antagonists (spironolactone, eplerenone).

1. Beneficial in patients already receiving therapeutic doses of ACEI or ARB and BB with LVEF ≤40% and either symptomatic heart failure or diabetes.
2. Avoid with renal insufficiency and/or hyperkalemia.

D. Nitrates.

1. Decrease myocardial demand by decreasing preload and afterload and increase oxygen supply by dilating coronary resistance vessels but have no mortality benefit.
2. Sublingual or intravenous nitrates beneficial for angina, heart failure, or hypertension.
3. Contraindicated in right ventricular infarction or with 5′phosphodiesterase inhibitor use within previous 24 hours.

E. Statins.

1. Statins should be initiated in all patients with goal LDL level <70 mg/dL.
2. High-intensity statin therapy reduces risk of death and ischemic events compared with moderate intensity therapy.

VII. COMPLICATIONS. See Tables 33-1 and 33-2.

VIII. OTHER CONSIDERATIONS

A. Acute kidney injury.

1. Risk factors include age, baseline renal function, IV contrast use, medications, and abnormal hemodynamics.
2. Prolongs hospital stay and contributes to adverse outcomes.

B. Glycemic control: Maintain blood glucose <180 mg/dL and avoid hypoglycemia.

1. Increased mortality with hypo- or hyperglycemia.
2. Glucose–potassium–insulin infusions not beneficial.

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STEMI patients randomized to ticagrelor versus clopidogrel in addition to standard therapy. The primary endpoint of cardiovascular death, MI, or stroke and secondary endpoint of all-cause mortality were reduced in ticagrelor-treated patients.

Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358:2218–2230.
In HORIZONS-AMI STEMI patients undergoing primary PCI were randomized to heparin plus glycoprotein IIb/IIIa inhibitor versus bivalirudin alone. A reduction in primary endpoint of major bleeding and net adverse clinical events was seen with bivalirudin monotherapy; secondary endpoint of 30-day mortality also reduced.

34 Complicated Myocardial Infarction

Srinath Adusumalli and Robert W. Yeh

I. BACKGROUND

A. Most complications of myocardial infarction (MI) and the highest associated mortality occur in the first few months after the acute event; therefore, prompt identification and treatment of any established or potential complications are necessary. An overview of the most common complications is presented in Table 34-1.

II. PATHOPHYSIOLOGY:

The proximate cause of ST elevation MI (STEMI) in most patients is acute coronary occlusion resulting from plaque rupture and platelet-initiated thrombosis. A non–ST elevation MI (NSTEMI) occurs when a **nonocclusive** thrombus develops. The sequelae of coronary occlusion are depicted in Figure 34-1.

III. PROGNOSIS AFTER MI

A. Incidence of complications has decreased in the reperfusion era. Recent registries indicate that the 30-day mortality following an STEMI is as low as 4.4%, whereas the mortality following an NSTEMI is 5%.

B. The thrombolysis in myocardial infarction (TIMI) study group recognized predictors of mortality after STEMI: age, low body weight, tachycardia, hypotension, history of hypertension, diabetes, or angina, time to treatment, anterior MI, MI with new left bundle branch block, and development of heart failure (HF). Similarly, they recognized the following predictors of mortality after NSTEMI: age, ≥3 CAD risk factors, known CAD with >50% stenosis, aspirin use in the last 7 days, severe angina in the last 24 hours, elevated cardiac markers, and ST deviation >0.5 mm.

C. An alternative index of mortality after either a STEMI or NSTEMI is the GRACE risk model that includes the following predictors: age, Killip class, systolic BP, presence of ST-segment deviation on admission, cardiac arrest at presentation, serum creatinine, elevated cardiac biomarkers, and heart rate.

IV. RECURRENT ISCHEMIA OR INFARCTION

A. Incidence and clinical consequences: Recurrent ischemic events after acute MI are a major cause of subsequent mortality. Reinfarction occurs in 4% to 10% of patients after thrombolytic therapy and 2% to 5% of patients after percutaneous coronary intervention (PCI) with most cases occurring within 4 days of hospital admission.

TABLE 34-1 Complications Following Acute MI

Recurrent infarction or ischemia	Infarct expansion Thinning and dilation of infarct segment without pain or CK leak Infarct extension Recurrent pain, ECG changes, and CK-MB leak
Left ventricular dysfunction	Acute Diastolic dysfunction may lead to pulmonary edema Systolic dysfunction may lead to cardiogenic shock and be a nidus for LV thrombus formation Chronic LV dilation and remodeling LV aneurysm and pseudoaneurysm LV thrombus
Inferior MI complications	RV infarct physiology Preload-dependent hypotension, increased JVP, and clear lungs; Kussmaul sign often present Heart block High-degree AV block
Mechanical complications	Free wall rupture VSD Papillary muscle rupture causing acute MR
Electrical disturbances and conduction disorders	Ventricular tachycardia and ventricular fibrillation Atrial fibrillation (10%–17% incidence) Conduction disorders and bradyarrhythmias
Miscellaneous	Complications of angiography and PCI such as access site bleeding, renal failure, vascular or coronary dissection, and cholesterol emboli syndrome Thromboembolism Pericarditis/Dressler syndrome

LV, left ventricle; CK, creatinine kinase; MB, MB fraction of creatinine kinase; ECG, electrocardiogram; RV, right ventricle; JVP, jugular venous pressure; AV block, atrioventricular block; VSD, ventricular septal defect; MR, mitral regurgitation; PCI, percutaneous coronary intervention.

B. The consequences of reinfarction with regard to short- and long-term mortality are grave. In the Multicenter Investigation of Limitation of Infarct Size (MILIS) study, patients who had infarct extension had an in-hospital mortality more than fourfold higher than patients without extension (30% vs. 7%, $p < 0.01$).

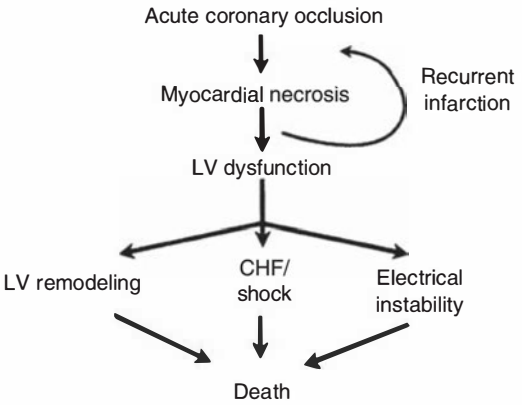

Figure 34-1. Sequelae of coronary artery occlusion. LV, left ventricle; CHF, congestive heart failure.

C. Prevention.

1. Antithrombotic therapy.

a. Platelet inhibition is one of the cornerstones of antithrombotic therapy in MI patients. Aspirin been shown to be of benefit across a wide spectrum of patients with ischemic heart disease. The antiplatelet agents clopidogrel, prasugrel, and ticagrelor provide further benefit when added to aspirin in patients with acute coronary syndrome (ACS), particularly those undergoing PCI.

b. Glycoprotein (GP) IIb/IIIa inhibitors are additional inhibitors of platelet aggregation and may be used in conjunction with PCI; in contrast, GP IIb/IIIa agents do not provide benefit when used with thrombolysis.

c. The next component of antithrombotic therapy for prevention of recurrent infarction is anticoagulation. Intravenous unfractionated heparin is necessary to maintain infarct-related artery patency in patients undergoing thrombolysis or PCI. Alternatives to UFH include low molecular weight heparin (LMWH), direct thrombin inhibitors (DTI) such as bivalirudin, and the pentasaccharide fondaparinux. Bivalirudin in particular has been shown to have similar ischemic outcomes and reduced bleeding as compared with UFH in patients with MI undergoing PCI.

2. β-Blockade has been studied extensively and has been found to be beneficial, especially among patients at highest risk, such as those with a history of HF or ventricular arrhythmias after MI. Oral β-blockade should be provided to all patients without contraindications (e.g., bradycardia, cardiogenic shock, severe HF, hypotension, second-/third-degree AV block). IV β-blockade may be given to those with tachyarrhythmias or uncontrolled severe hypertension (in the absence of contraindications), although care must be given as beta-blocker treatment in the acute setting may increase the risk of HF or shock.

D. Treatment: An approach to the acute evaluation and treatment of recurrent ischemic events is outlined in Figure 34-2.

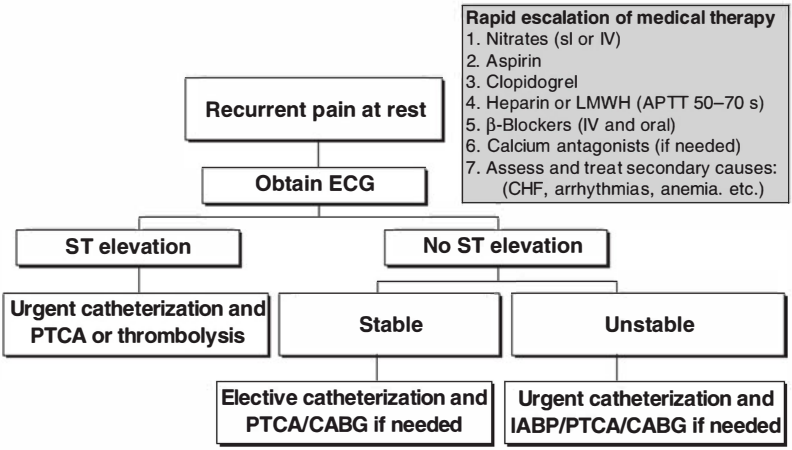

Figure 34-2. An approach to the acute evaluation and treatment of recurrent ischemic events. Sl, sublingual; IV, intravenous; LMWH, low molecular weight heparin; APTT, automated partial thromboplastin time; CHF, congestive heart failure; ECG, electrocardiogram; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; IABP, intraaortic balloon pump.

V. RIGHT VENTRICULAR INFARCTION

A. Background: Right ventricular (RV) infarction occurs clinically in approximately 30% of patients with inferior MI (themselves accounting for more than half of all MIs), but only in half of those cases is it clinically relevant.

B. Pathophysiology.

1. RV infarction is caused by very proximal occlusion of the right coronary artery.
2. A loss of contractile performance of the RV—a thin-walled chamber—results in reduced left ventricular (LV) preload and systemic hypotension. The associated diastolic abnormalities cause systemic venous hypertension.
3. Atrioventricular (AV) or sinoatrial (SA) nodal block occurs in 10% to 15% of patients with inferior MI but is particularly prevalent in those with RV infarction; approximately 25% of patients with inferior MI with RV involvement develop conduction system disease.

C. Clinical presentation.

1. Jugular venous distension (JVD) and clear lungs distinguish RV infarction from combined right- and left-sided congestion resulting from LV dysfunction.
2. Systemic hypotension is a frequent complication of RV infarction, in which poor RV output leads to decreased LV filling.
3. Right-sided electrocardiogram (ECG) may facilitate diagnosis. ST elevations in lead V4R in particular should raise suspicion. Precordial ST-segment depressions can be seen on the ECG of patients with RV

infarction in 15% to 30% of cases and must be differentiated from anterior ischemia.

4. The differential diagnosis for RV infarction includes hypotension resulting from LV infarction, pericardial tamponade, constrictive pericarditis, and pulmonary embolism (PE).

D. Treatment.

1. Initial treatment of RV infarction involves early reperfusion therapy directed at limiting infarct size.
2. Volume expansion is the mainstay of therapy in patients with hypotension, with the aim of a right atrial or central venous pressure as high as necessary to fill the LV adequately. A central venous pressure value up to 15 to 20 mm Hg is acceptable.
3. If volume expansion alone does not restore systemic blood pressure to >90 mm Hg, dobutamine or dopamine should be used to increase RV output.
4. In contrast to left-sided HF, for isolated right-sided HF, venous vasodilators such as nitrates (and to a lesser extent morphine) should be avoided.
5. If hemodynamically significant sinus bradycardia or AV block develops, temporary ventricular pacing may be necessary.

VI. LEFT VENTRICULAR DYSFUNCTION (PUMP FAILURE)

A. Background.

1. The most important determinant of prognosis after MI is the degree of LV dysfunction.
2. The following factors influence residual ventricular function.
   a. LV function before the acute MI.
   b. Infarct size.
   c. Infarct location.
3. Cardiogenic shock occurs in approximately 7% of MI cases and is the most malignant end of the spectrum of HF. Such patients with systemic hypoperfusion and pulmonary congestion have the highest risk of death after MI (inhospital mortality approaches 50%).

B. Pathophysiology.

1. The clinical consequence of myocardial injury is HF. There may be systolic dysfunction, manifested by reduced systemic perfusion and evidence of pulmonary congestion, or diastolic dysfunction, manifested by increases in LV filling pressures and pulmonary congestion, but less evidence of reduced systemic perfusion. Shock typically results from massive MI or severe ischemia leading to a sudden and substantial decline in cardiac output.
2. Diastolic dysfunction occurs almost uniformly in patients with acute MI, although it becomes clinically significant in only one-fourth to one-third of such patients. It is the most common cause of early mild HF in the setting of acute MI and can be responsible for acute pulmonary edema.

C. Treatment.

1. The initial goals of treatment for MI complicated by HF are to
   a. Ensure adequate oxygenation with supplemental oxygen (and endotracheal intubation, if necessary).
   b. Maintain systolic blood pressure at 90 mm Hg or greater (MAP >65 mm Hg).
   c. Ensure adequate perfusion of vital organs.
   d. Administration of diuretics and/or nitrates diminishes pulmonary congestion and reduces ventricular filling pressures; caution must be taken to avoid excessive preload reduction, which may compromise systemic perfusion (target PCWP 15 to 20 mm Hg).
   e. Management may be aided by pulmonary artery catheterization in those patients with persistent, refractory hypotension and in those on inotropic and pressor support.
2. Caution with use of β-blockers for patients with acute decompensated HF and systolic dysfunction who may not tolerate the negative inotropic effects.
3. Inotropes or mechanical circulatory support may be needed to manage cardiogenic shock. Please see Chapter 25 for a detailed discussion.
4. Early reperfusion of the infarct-related artery is a high priority in patients with MI complicated by shock. Early, emergent angiography and revascularization should be considered, particularly for patients younger than 75 years.

VII. MECHANICAL COMPLICATIONS

A. Background.

1. Mechanical complications after an MI include ventricular septal rupture (VSR, see Fig. 34-3 and Video 34-1), rupture of the ventricular free wall (Fig. 34-4), and rupture of the papillary muscle (Fig. 34-5 and Video 34-2). The incidence of these complications has decreased significantly with the advent of PCI. When they occur, the time course for these complications has a bimodal peak, with one peak within 24 hours of MI and a second peak 3 to 5 days post-MI. Table 34-2 summarizes the clinical profiles manifested in the various mechanical complications of MI.

B. Prognosis: Mechanical complications, particularly LV free wall rupture, are associated with mortality rates exceeding 80%. Prompt surgical repair of free wall rupture can improve outcome.

C. Diagnosis.

1. A high index of suspicion is required for patients with hypotension, severe HF, cardiogenic shock, or an unexplained change in clinical status, especially if a new systolic murmur is present.
2. Transthoracic echocardiography is the diagnostic test of choice in patients with suspected ventricular rupture. VSR can be differentiated from papillary muscle rupture leading to MR on the basis of right heart oximetric data with a step-up in oxygen saturation between the right

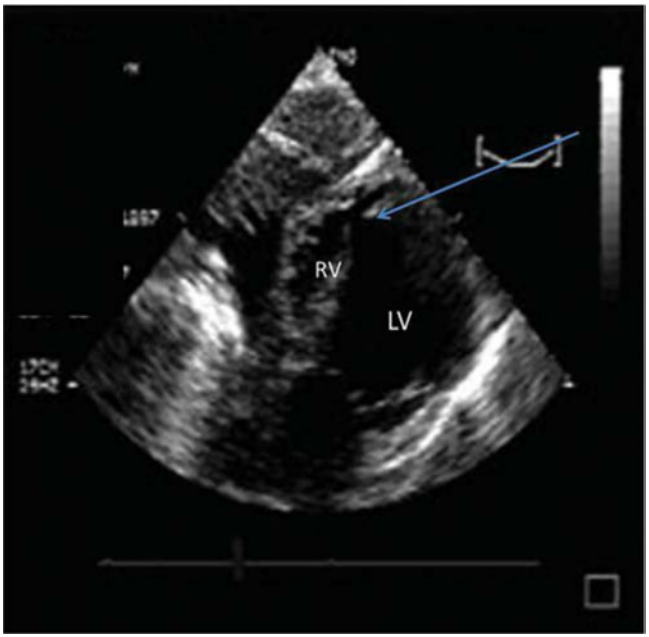

Figure 34-3. Subcostal four-chamber view of transthoracic two-dimensional echocardiogram in a 68-year-old woman who developed shock 2 weeks after extensive MI. A rupture of the ventricular septum is noted *(arrow)*. LV, left ventricle; RV, right ventricle.

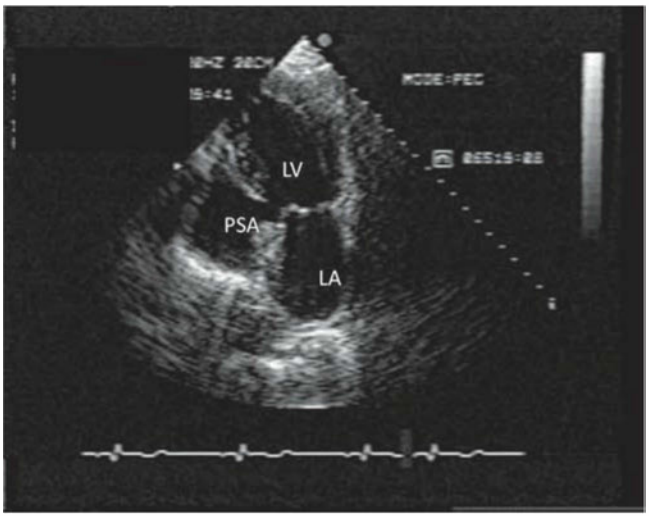

Figure 34-4. Apical two-chamber view of a transthoracic two-dimensional echocardiogram in a 55-year-old man who collapsed 6 months after inferior MI. The image shows a left ventricular free wall rupture resulting in pseudoaneurysm (PSA) communicating with the left ventricle (LV). LA, Left atrium.

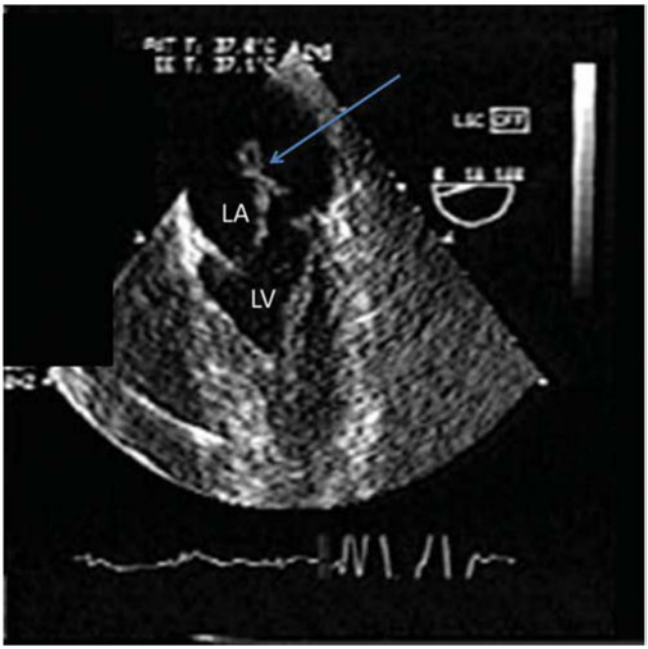

Figure 34-5. Two-dimensional transesophageal echocardiogram in a patient undergoing mitral valve replacement for a ruptured papillary muscle (*arrow*). LV, left ventricle; LA, Left atrium.

atrium and right ventricle. A new systolic murmur is a clinical feature of VSD and MR.

D. Treatment.

1. Pericardiocentesis is potentially lifesaving in patients with free wall rupture but should not delay surgical repair.
2. Supportive measures, IABP placement, and prompt surgical intervention are mainstays of treatment in patients with MR or VSR.

VIII. THROMBOEMBOLISM

A. Background: LV mural thrombus formation is a well-recognized complication of acute MI, occurring in up to 40% of patients in the pre-reperfusion era and now occurring in 4% to 10% of patients treated with fibrinolysis or PCI, especially after a large anterior–apical MI. Both arterial and venous emboli can occur, with LV mural thrombi accounting for most arterial emboli and RV or deep venous thrombi leading to PE.

TABLE 34-2 Clinical Profiles of Mechanical Complications in Acute MI

Variable	VSR	Free wall rupture	Papillary muscle rupture
Incidence	~1%–3% in prethrombolytic era; 0.2%–0.34% in reperfusion era, 3.9% among those with cardiogenic shock	0.8%–6.2% of MI (<1% with reperfusion)	1%
Risk factors	Age, female, no prior MI, total occlusion with minimal collaterals	Female, first MI, AS, HTN, steroids, NSAIDs	Common in small infarctions, inferoposterior infarctions, less CAD, good LVEF
Time course	Bimodal peak; within 24 h and 3–5 d (range, 1–14 d)	Bimodal peak; within 24 h and 3–5 d (range, 1–14 d)	Bimodal peak; within 24 h and 3–5 d (range, 1–14 d)
Anterior MI	66%	50%	25%
New murmur	90%	25%	50%
Palpable thrill	Yes	No	Rare
Previous MI	0%–25%	25%	30%
Echocardiographic findings 2-D	Location, size of VSR, L–R shunt, RV overload	Visualizes defect, presence of hemopericardium	Flail leaflet, severe mitral regurgitation
PA catheterization	O_2 step-up in RV	Equalization of diastolic pressures (but not always present)	Prominent V wave in PCWP pressure tracing
Medical mortality	90%	90%	90%
Surgical mortality	42%–75%	Case reports of success	40%–90%

VSR, ventricular septal rupture; AS, aortic stenosis; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; PA, posteroanterior; RV, right ventricular; PCWP, pulmonary capillary wedge pressure.
Adapted from Braunwald E, Bonow RO. *Braunwald's heart disease: A textbook of cardiovascular medicine,* 9th ed. Philadelphia: Elsevier Saunders, 2012:1961, 56. http://nrs.harvard.edu/urn-3:hul.ebook:MDCON_11301957.

B. Treatment.

1. Anticoagulation represents first-line therapy and is usually continued for 3 to 6 months. Echocardiography is routinely performed to evaluate resolution and stability.
2. Fibrinolytic therapy may be considered in patients with cardioembolic stroke but should be undertaken with great caution.

IX. PERICARDITIS

A. Background: Pericardial irritation occurs in approximately one-fourth of patients with acute MI and usually begins 1 to 4 days after MI. It is far more common with ST-elevation MI than with NSTEMI.

B. Diagnosis: Pericarditis may present as an asymptomatic pericardial effusion, early symptomatic pericarditis with or without effusion, or late pericarditis (an autoimmune phenomenon known as Dressler syndrome and occurs 2 to 10 weeks post-MI). It is usually accompanied by a pericardial rub.

1. Aspirin is given to relieve pain and to decrease inflammation; up to 650 mg every 4 hours may be required. The use of acetaminophen or colchicine can also be considered.
2. Other nonsteroidal anti-inflammatory medications relieve pain but may lead to infarct thinning and coronary artery vasoconstriction and may interfere with antiplatelet effect of aspirin.
3. Corticosteroids should be avoided as they can induce scar thinning and rupture.
4. Minimizing anticoagulation to avoid hemorrhagic pericarditis is recommended.

X. ARRHYTHMIAS COMPLICATING MI

A. Background.

1. In the prehospital phase, ventricular tachycardia and fibrillation probably account for the majority of sudden deaths.
2. Tachyarrhythmias and bradyarrhythmias are frequently seen in the in-hospital phase of acute MI.

B. Pathophysiology: Arrhythmias in the setting of acute MI may be due to reentry, abnormal automaticity, or conduction block; these mechanisms are modulated by ischemia, LV failure, and variations in autonomic tone. Arrhythmias and their treatment are outlined in Tables 34-3 and 34-4.

C. Indications for pacemaker placement during MI (see Chapter 37).

D. Prophylactic implantation of implantable cardioverter–defibrillator (ICD) is recommended in convalescent phase post-MI if EF is <35% on a 40-day post-MI echocardiogram.

E. Always ensure potassium is repleted >4.0 mEq/L and magnesium is repleted >2.0 mEq/L.

TABLE 34-3 Arrhythmias during Acute MI

Category	Arrhythmia	Objective of therapy	Therapeutic options
Ventricular tachycardias (VT)	Ventricular fibrillation	Urgent reversion to perfusing rhythm	Defibrillation; amiodarone, Lidocaine
	VT	Restoration of normal sinus rhythm (NSR)	Cardioversion/defibrillation; amiodarone, lidocaine, procainamide
	Accelerated idioventricular rhythm (AIVR)	Observation unless hemodynamically unstable	Increase sinus rate with atropine; atrial pacing
Supraventricular tachycardias (SVT)	Sinus tachycardia	When appropriate, reduction of rate to diminish O_2 demand	Identify and treat underlying cause.
	Atrial fibrillation or atrial flutter (AF)	Reduction of ventricular rate, restoration of NSR	Cardioversion when unstable; β-blockers, calcium channel blockers, digoxin; consider amiodarone.
	Paroxysmal SVT	Reduction of ventricular rate, restoration of NSR	Vagal maneuvers; adenosine same as AF
	Nonparoxysmal junctional tachycardia	Reduction of ventricular rate, restoration of NSR	Search for precipitating cause (e.g., digitalis toxicity); observe and consider overdrive atrial pacing or antiarrhythmics if unstable.
Bradyarrhythmias	Sinus bradycardia	Increase heart rate (HR) only if hemodynamically compromised	Atropine; temporary pacing
	Junctional escape	Increase HR only if loss of "atrial kick" leads to hemodynamic compromise	Atropine; temporary pacing
	High-degree AV block	Increase HR	Atropine, aminophylline; temporary pacing

Adapted from Antman EM., Morrow DA. ST-segment elevation myocardial infarction: management. In: Braunwald E, Bonow RO. *Braunwald's heart disease: A textbook of cardiovascular medicine*, 9th ed. Philadelphia: Elsevier Saunders, 2012:1961, 56. http://nrs.harvard.edu/urn-3:hul.ebook:MDCON_11301957.

TABLE 34-4 ACLS Intravenous Antiarrhythmic Drug Dosing

Drug	Bolus	Infusion
Lidocaine	1.0–1.5 mg/kg initially; additional boluses (0.5–0.75 mg/kg every 5–10 min) as necessary to control VT/VF to maximum total load 3 mg/kg	1–4 mg/min
Procainamide	15–18 mg/kg (maximum 1,000 mg) over 25–30 min	1–4 mg/min (reduce dose in the presence of severe cardiac/renal impairment)
Amiodarone	150 mg over 10 min for SVT, 300 mg for VT/VF. Can repeat second dose of 150 mg if needed	1 mg/min for 6 h, then 0.5 mg/min for 18 h, then transition to oral dosing

ACKNOWLEDGMENTS

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35 Ventricular Tachycardia

Bruce A. Koplan and William G. Stevenson

I. GENERAL PRINCIPLES

A. Definitions.

1. **Ventricular tachycardia (VT).**
   - **a.** ≥3 beats at a rate ≥100 bpm.
   - **b.** QRS width ≥0.12 seconds.
   - **c.** Originates from the ventricle.
2. **Nonsustained ventricular tachycardia (NSVT).**
   - **a.** Terminates spontaneously within 30 seconds without causing severe symptoms.

B. Classification (Fig. 35-1).

1. **Monomorphic VT.** Same configuration from beat to beat.
   - **a.** Usually due to a circuit through a region of old myocardial infarction (MI) scar.
   - **b.** Idiopathic VT (less common): VT in the absence of an identifiable cause (e.g., structural heart disease/prior MI).
     - **i.** Right ventricular outflow tract (RVOT) tachycardia: most common idiopathic VT. Left bundle branch block morphology with inferior axis.
2. **Polymorphic VT.** Continually changing QRS morphology.
   - **a. Etiologies.**
     - **i.** Active cardiac ischemia (most common).
     - **ii.** Electrolyte disturbance.
     - **iii.** Drug toxicity.
     - **iv.** Familial.
   - **b.** ***Torsade de pointes.***
     - **i.** Unique form of polymorphic VT.
     - **ii.** Waxing and waning QRS amplitude during tachycardia associated with prolonged QT interval.
     - **iii.** Secondary to QT-prolonging drugs, electrolyte abnormalities, or familial ion channel disorders (long QT syndrome).
3. **Sinusoidal VT.** Sinusoidal appearance often associated with severe electrolyte disturbance (e.g., hyperkalemia).
4. **Accelerated idioventricular rhythm (AIVR).**
   - **a.** Wide complex, ventricular rhythm at 40 to 100 beats/min.
   - **b.** Usually hemodynamically stable.
   - **c.** Can occur in the first 12 hours after reperfusion of an acute MI or during periods of elevated sympathetic tone.

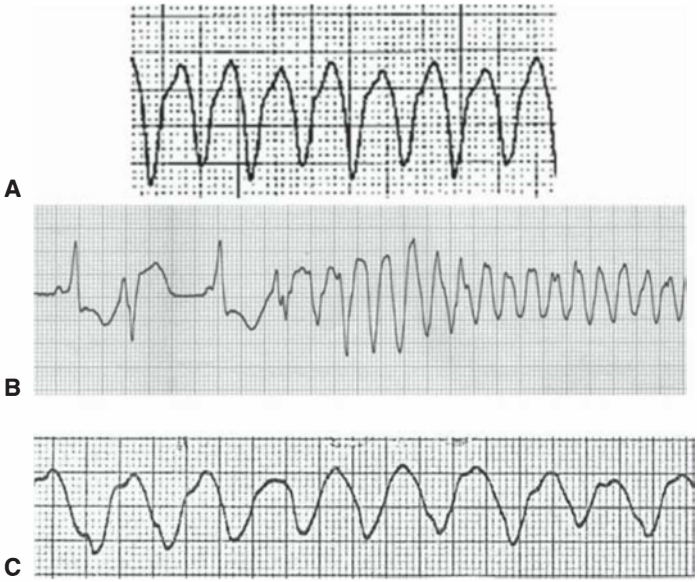


Figure 35-1. Three different wide QRS tachycardias are shown: monomorphic VT in **(A)**; polymorphic VT in **(B)**; and sinusoidal VT due to hyperkalemia in **(C)**.

d. Onset typically preceded by sinus slowing.
e. Usually resolves without specific therapy.
f. Antiarrhythmic drug (AAD) treatment rarely necessary.

II. DIAGNOSIS

A. Differentiating VT from supraventricular tachycardia (SVT) in a patient with a wide complex tachycardia (WCT).

1. **Differential diagnosis of WCT.**
   a. VT.
   b. SVT with aberrancy (bundle branch block).
   c. SVT conducting down an accessory pathway (Fig. 35-2B).
2. Assume VT until proven otherwise.
3. WCT with a history of MI should be assumed to be VT unless proven otherwise.
4. If the patient is hemodynamically stable, obtain a 12-lead electrocardiogram (ECG).
5. **ECG criteria** that favor VT over SVT (Fig. 35-3A and B).
   a. AV dissociation (Figs. 35-2A and 35-4).
   b. Initial R in avR.
   c. QRS concordance. Absence of an rS or Rs complex in any precordial lead (V_1-V_6).
   d. Capture beats/fusion beats during tachycardia (Fig. 35-4).

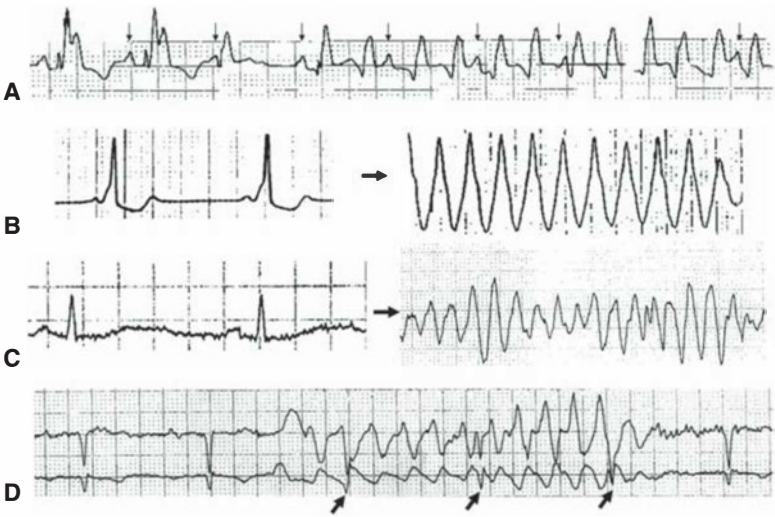


Figure 35-2. WCTs. **A:** Transition from sinus rhythm to VT with AV dissociation (P waves identified by *small arrows*). **B:** Short PR and delta wave during sinus rhythm on left, and atrial fibrillation with rapid, irregular, wide complex ventricular response due to conduction over the accessory pathway in a patient with the WPW syndrome. **C:** The polymorphic VT *torsade de pointes* (**right side**) in a patient with QT prolongation (**left side**). **D:** Motion artifact mimicking a WCT. Note that within the artifact, QRS complexes (*large arrows*) are present occurring at the same interval as before and after the onset of the artifact waveform. AV, atrioventricular; VT, ventricular tachycardia.

i. Occur when a supraventricular conducts to the ventricles, depolarizing the ventricle (completely—capture beat or partially—fusion beat) in advance of the next tachycardia beat.

ii. Morphologically identical (capture beat) or similar (fusion beat) to the QRS complex seen in sinus rhythm but occur in the midst of a wide QRS complex tachycardia.

iii. Capture beats during WCT are pathognomonic for VT.

6. Additional principles.

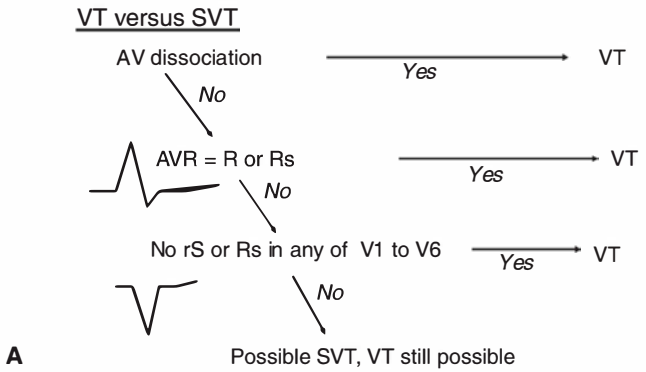
a. Hemodynamic instability is dependent on the rate and underlying ventricular function and does not differentiate VT from SVT.

b. **Electrocardiographic artifacts** can mimic VT/ventricular fibrillation (VF) (Fig. 35-2D).

III. TREATMENT. First priority—Determine whether the patient is hemodynamically stable.

A. Management of hemodynamically unstable VT/VF (see Algorithm, Fig. 35-5).

1. CPR and rapid defibrillation are the most important measures to improve survival.



A

Wide Complex Tachycardia:
Additional ECG/clinical findings supporting VT vs. SVT

Characteristic	Favors VT	Favors SVT
Capture beats or fusion beats	+	
Prior known MI or CMP	+	
Irregularly irregular		+
History of WPW, prior delta wave in SR		+
Onset with a PAC or SVT with similar rate		+
Identical QRS during SR in a patient with preexisting BBB		+

B

Figure 35-3. **A:** Electrocardiographic features to differentiate VT versus SVT in patients presenting with wide QRS complex tachycardia. VT, ventricular tachycardia; SVT, supraventricular tachycardia; AV, atrioventricular; RBBB, right bundle branch block; LBBB, left bundle branch block. (Modified from Vereckei A, Duray G, Szenasi G, et al. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. *Heart Rhythm* 2008;5:89–98). See text for details. **B:** Additional clinical and ECG findings to assist with differentiation between ventricular tachycardia (VT) and supraventricular tachycardia (SVT) in patients with WCT. See text for details. ECG, electrocardiogram; MI, myocardial infarction; CMP, cardiomyopathy; PAC, premature atrial contraction; SR, sinus rhythm; IHD, ischemic heart disease; RBBB, right bundle branch block; LBBB, left bundle branch block.

2. AADs—see III.B.1 in subsequent text.

a. Used when cardioversion fails or VT/VF recurs.

b. *Amiodarone* (often used as first-line therapy), *Procainamide* (alternative to amiodarone), *lidocaine* (most appropriate during suspected acute myocardial ischemia).

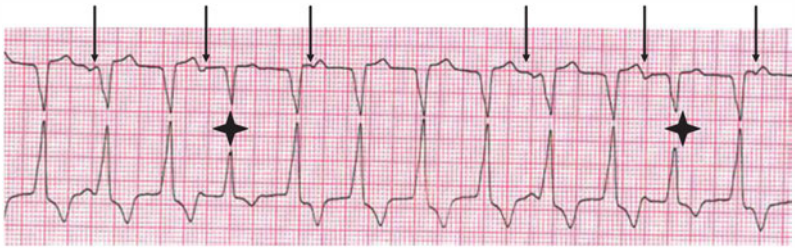


Figure 35-4. Ventricular tachycardia with AV dissociation (arrows showing p waves) and capture beats during ventricular tachycardia (asterisks). See text for details.

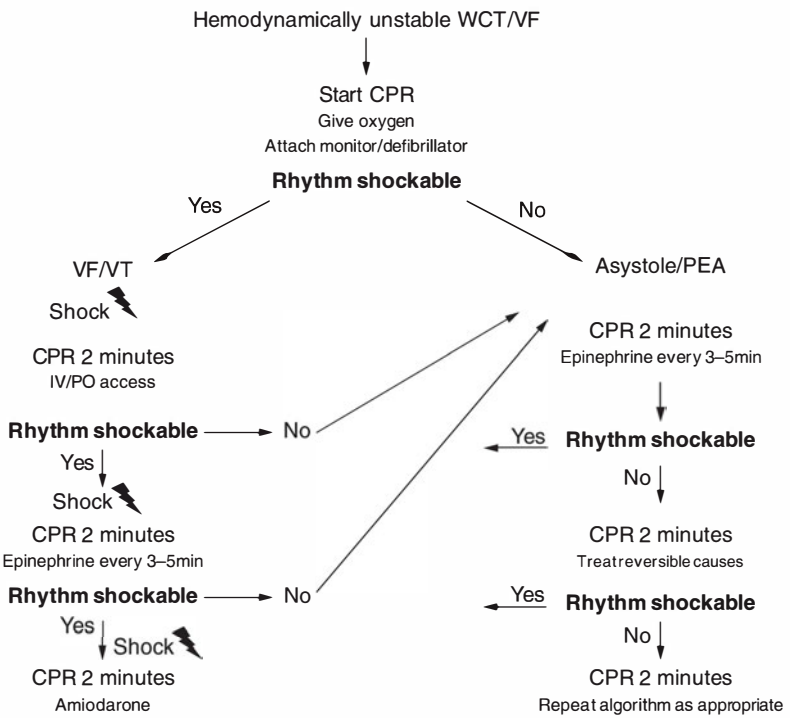


Figure 35-5. Approach to unstable WCT/VF. This algorithm assumes that CPR is initiated after the three unsuccessful shocks and maintained until a pulse is achieved. VF, ventricular fibrillation; PMVT, polymorphic ventricular tachycardia; VT, ventricular tachycardia; Amio, amiodarone; Epi, epinephrine; MVT, monomorphic ventricular tachycardia; CPR, cardiopulmonary resuscitation.

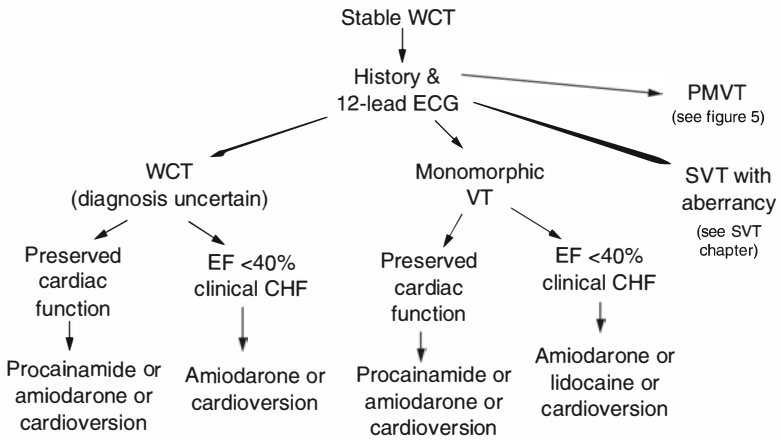


Figure 35-6. Approach to stable WCT. WCT, wide complex tachycardia; ECG, electrocardiogram; EF, ejection fraction; CHF, congestive heart failure; VT, ventricular tachycardia; PMVT, polymorphic ventricular tachycardia; SVT, supraventricular tachycardias. See text for details.

B. Management of hemodynamically stable WCT (see Algorithm, Fig. 35-6).

1. **AADs.**
   - **a.** Amiodarone.
   - **b.** Procainamide.
   - **c.** Lidocaine.
2. **Electrical cardioversion** is also an appropriate initial therapy.
3. If Wolff-Parkinson-White (WPW) syndrome (see Chapter 38) is suspected (Fig. 35-2B), intravenous procainamide or cardioversion are first-line therapies.

C. Management of polymorphic VT/sinusoidal VT.

1. Correct reversible causes
   - **a.** Cardiac ischemia.
   - **b.** Metabolic abnormalities.
   - **c.** Drug toxicity including QT-prolonging drugs.
2. Lidocaine and amiodarone can be considered for recurrent episodes.
3. Treatment of *torsade de pointes* (polymorphic VT due to QT prolongation).
   - **a.** Intravenous magnesium sulfate (1 to 2 g) (can be repeated).
   - **b.** Correct electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia).
   - **c.** Discontinue QT-prolonging medications.
   - **d.** Increasing heart rate with **pacing** or **isoproterenol** can be highly effective. Transvenous temporary ventricular pacing is most reliable (target rate of 110 to 120 bpm). Isoproterenol should not be used if congenital long QT syndrome is suspected.

D. Implantable cardioverter–defibrillators (ICDs).

1. For some patients at high risk for VT/VF, ICDs should be considered for long-term protection after acute issues resolve provided that acceptable functional recovery and survival for more than 1 year is anticipated.
   a. ICDs for primary prevention of sudden death should be considered for patients who have not had spontaneous sustained VT/VF but have the following risks factors.
      i. Persistently reduced ejection fraction ≤35% due to either ischemic or nonischemic cardiomyopathy, genetic diseases associated with sudden death (e.g., some hypertrophic and familial cardiomyopathies).
      ii. ICDs for secondary prevention of sudden death after resuscitation from VT/VF are recommended if the arrhythmia is not due to a correctable, reversible cause, such as acute MI or drug toxicity.

E. Management of NSVT/ventricular ectopy: "first do no harm".

1. NSVT/premature ventricular contractions (PVCs) are common in the intensive care unit (ICU).
2. Treatment.
   a. Correct possible aggravating factors (e.g., ischemia, electrolyte disturbance, hypoxia, hypoventilation, beta-agonists).
   b. β-Blocking agents (if not contraindicated).
   c. In the absence of symptoms, administration of antiarrhythmic agents should be avoided and may increase mortality.

F. Electrical storm: defined as three or more episodes of VT or VF in a 24-hour- period.

1. May be managed with AADs.
2. Catheter ablation can be an effective option with acceptable risk.

IV. OVERVIEW OF DRUGS COMMONLY USED FOR THE MANAGEMENT OF VT/VF IN THE ICU

A. General principles.

1. Narrow toxic–therapeutic relationship and potential for proarrhythmia necessitates careful monitoring.
2. Titration to achieve the desired effect is often required.

B. β-*Blockers* (Class II).

1. Indications.
   a. Symptomatic ventricular ectopy.
   b. Recurrent sustained ventricular tachyarrhythmias. The frequency of VT/VF (electrical storm) is often aggravated by high sympathetic tone and may improve with β-adrenergic blockade.
2. Short-acting agents (e.g., metoprolol tartrate) are preferable in the ICU setting.
   a. *Metoprolol.*
      i. Can be given orally or as a 5-mg slow intravenous push and repeated every 5 to 10 minutes up to a total of 20 mg IV. Can

repeat intravenous boluses every 4 to 6 hours or oral dosing every 4 to 8 hours.

ii. *Esmolol* (useful when there is concern that a β-blocker may be poorly tolerated) (short half-life 2 to 9 minutes).

(a) 500 μg/kg IV bolus over 1 minute followed by a maintenance dose of 50 μg/kg/min titrated for effect up to 300 μg/kg/min.

3. Adverse effects of β-blockers.
   a. Negative inotropy (avoid with decompensated heart failure).
   b. Bradycardia.
   c. Aggravation of bronchospasm.

C. *Amiodarone.*

1. Indications.
   a. First-line AAD in advanced cardiac life support (ACLS) VF/pulseless VT algorithm.
   b. Hemodynamically stable VT that recurs after cardioversion or fails IV procainamide.
2. Dosing.
   a. A 150- to 300-mg IV bolus over 10 minutes, followed by an infusion at 1 mg/min for 6 hours and then 0.5 mg/min.
   b. Additional 150-mg boluses can be given for breakthrough arrhythmia up to a total load of approximately 2 g/24 hours and 5 to 8 g total.
   c. Can also be loaded orally (800 to 1,600 mg daily for 2 to 3 weeks, with maintenance dose of 400 mg daily for ventricular arrhythmias).
3. Adverse effects.
   a. Even though amiodarone causes QT prolongation, *torsade de pointes* and other proarrhythmic complications are rare.
   b. Hypotension during intravenous administration.
   c. Bradycardia.
   d. Exacerbation of congestive heart failure (negative inotropic effect).
   e. Phlebitis (when administered through a peripheral intravenous line). Continuous infusions should be administered through a central venous catheter.
   f. Other adverse effects include hepatitis, hyper- or hypothyroidism, pneumonitis, neuropathy, and tremor.

D. *Procainamide.*

1. First-line agent for WCT (along with amiodarone) for the treatment of hemodynamically stable WCT and WCT due to WPW syndrome.
2. Alternative agent for hemodynamically unstable WCT and VF.
3. Dosing: 20 to 30 mg/min IV infusion loading dose up to a total initial dose of 10 to 17 mg/kg, followed by a maintenance infusion of 1 to 4 mg/min.
4. Adverse effects.
   a. Vasodilatation and negative inotropy.
      i. Avoid with depressed ventricular function (ejection fraction <40%) in favor of amiodarone.
      ii. Blood pressure should be monitored carefully during IV administration.

b. *N*-acetyl-procainamide (NAPA), a metabolite of the drug, can increase QTc and cause *torsade de pointes*.
  i. Monitor serum procainamide and NAPA levels if the drug is continued for >24 hours.
  ii. QTc interval and QRS complex width should be monitored.
    (a) Discontinue if the QRS widens by >50% from baseline.
c. Avoid in patients with significant renal dysfunction.
  i. NAPA is excreted entirely by the kidney.

E. *Lidocaine* (IB).

1. Indications.
  a. Acute management of life-threatening ventricular arrhythmias, especially when associated with myocardial ischemia. Amiodarone, procainamide, and β-blockers are preferable.

2. Dosing: 1 to 1.5 mg/kg IV bolus. Can repeat to a maximum bolus of 3 mg/kg, followed by an infusion of 1 to 4 mg/min.

3. Adverse effects.
  a. Minimal adverse hemodynamic side effects.
  b. Neurologic toxicity (seizures, tremors, and confusion).

4. Class IC AADs (***flecainide, propafenone***) are rarely used in the ICU for VT/VF due to proarrhythmia and negative inotropic risks. They increase long-term mortality in patients with coronary artery disease and depressed ventricular function.

SUGGESTED READINGS

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36 Supraventricular Tachycardia

John L. Sapp Jr and Laurence M. Epstein

I. BACKGROUND

A. Definition: Supraventricular tachycardias are those arrhythmias that require involvement of the atrioventricular (AV) node or atria for their perpetuation. They are usually described by mechanism or by their electrocardiographic appearance (Figs. 36-1 and 36-2).

II. MECHANISMS: **There are two main mechanisms underlying supraventricular tachycardias.**

A. Focal Arrhythmias: for example, inappropriate sinus tachycardia, ectopic atrial tachycardia, atrial premature beats, multifocal atrial tachycardia.

B. Reentry: for example, atrioventricular reentrant tachycardia (AVRT), atrioventricular nodal reentrant tachycardia (AVNRT), atrial flutter.

III. RECOGNITION AND DIAGNOSIS (see Figs. 36-1 and 36-2).

It should be noted that rate or hemodynamic stability does not predict the tachycardia mechanism. Rapid, poorly tolerated rhythms can be SVT, and slower, well-tolerated rhythms can be ventricular tachycardia (VT).

A. QRS is >120 ms (wide complex tachycardia).

1. Supraventricular activation with aberrancy or preexcitation (over an accessory AV pathway) will result in a wide complex tachycardia. This must be distinguished from ventricular tachycardia.

2. The presence of a history of significant structural heart disease or a QRS morphology atypical for bundle branch block increases the likelihood of VT. Consultation should be sought.

B. QRS duration <120 ms in *all* surface leads: likely supraventricular.

C. Irregularly irregular QRS complexes most commonly signify atrial fibrillation (multifocal atrial tachycardia is distinguished by the presence of P waves with at least three different morphologies).

D. Irregularly irregular rhythm with wide/varying QRS width may suggest atrial fibrillation with ventricular preexcitation over an accessory pathway (AP) (this is uncommon).

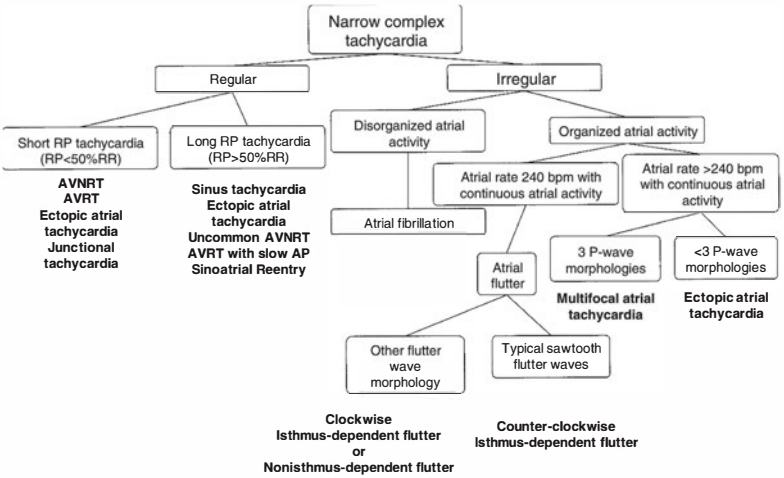

Figure 36-1. Electrocardiographic classification of supraventricular tachycardia.

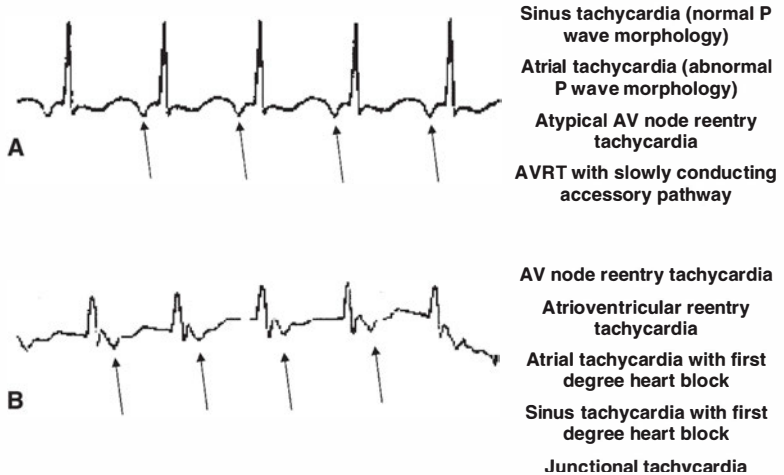

Figure 36-2. Diagnosis of regular narrow complex tachycardias. **A:** The RP interval (P waves indicated by *arrows*) is longer than the PR interval. The differential diagnosis is sinus tachycardia (which is associated with a normal or near normal P wave morphology), ectopic atrial tachycardia (which usually has a sudden start/stop and may have an abnormal P wave morphology), atypical atrioventricular (AV) node reentry tachycardia (in which antegrade propagation is via the "fast pathway" and retrograde activation is via the "slow pathway"), or AV reentry tachycardia utilizing a slowly conducting AP. **B:** The RP interval (P waves indicated by *arrows*) is shorter than the PR interval. The differential diagnosis is typical AV nodal reentry tachycardia, AV reentry tachycardia, ectopic or sinus tachycardia with first-degree heart block (PR prolongation), or junctional tachycardia.

E. Atrial activity.

1. The P waves may be buried in the QRS–T complex. If possible, compare to sinus rhythm tracings to look for subtle manifestations of atrial activation (r′ in lead V1 or small S wave in inferior leads).
2. Organized continuous atrial activity >240 beats/min is classified as atrial flutter. Typical atrial flutter: downsloping flutter waves in the inferior leads followed by a rapid upstroke, short positive P waves in V1, and an atrial rate of approximately 300 beats/min. Atypical flutter circuit or ectopic atrial tachycardia may have a different morphology or atrial rate.
3. If every P wave is not associated with a QRS (i.e., AV block is present), the tachycardia is unlikely to depend on the AV node. Differential diagnosis: ectopic atrial tachycardia, atrial flutter, can very rarely be seen with AVNRT.
4. Is there a 1:1 relationship between P and QRS deflections? (See Fig. 36-2.) Is there a long RP (RP > PR) tachycardia (differential diagnosis: ectopic atrial tachycardia, sinus tachycardia, less commonly AVRT utilizing a slowly conducting bypass tract or atypical AVNRT) or a short RP tachycardia (RP < PR; differential diagnosis: AVNRT, AVRT, junctional tachycardia, or ectopic atrial tachycardia)?

IV. GENERAL MANAGEMENT OF SUPRAVENTRICULAR TACHYCARDIAS:

A general approach to the evaluation and management of supraventricular tachycardias is outlined in Figure 36-3.

A. Assess patient stability.

B. Identify sinus tachycardia or multifocal atrial tachycardia if present: Treat the underlying causes and control heart rate.

C. If unstable: Prompt direct current (DC) cardioversion.

1. Electrical cardioversion should be synchronized. Atrial flutter and other SVTs are usually terminable with a single 50- to 100-J countershock. Atrial fibrillation often requires 200 to 360 J.

D. Stable patients.

1. Vagal maneuvers: carotid sinus massage or a Valsalva maneuver (can also be diagnostic by causing transient AV block unmasking P or flutter waves).
2. Adenosine: 6 to 12 mg, rapid IV push, followed by immediate saline flush. Carbamazepine and dipyridamole potentiate the actions of adenosine and may prolong its action causing angina or bronchospasm. Methylxanthines (caffeine, theophyllines) antagonize the effects of adenosine and may render it ineffective. Consider lower dose if administered centrally or in heart transplant recipients.
3. IV verapamil, diltiazem, or β-blockers may be used (Table 36-1). Vagal maneuvers may be repeated in the presence of drug therapy and may act synergistically.
4. Atrial flutter, atrial tachycardia, and atrial fibrillation are unlikely to terminate with these measures, although flutter waves or ectopic P waves may be unmasked, facilitating diagnosis.
5. Type I or type III antiarrhythmic agents may be used for conversion alone or in combination with DC cardioversion.

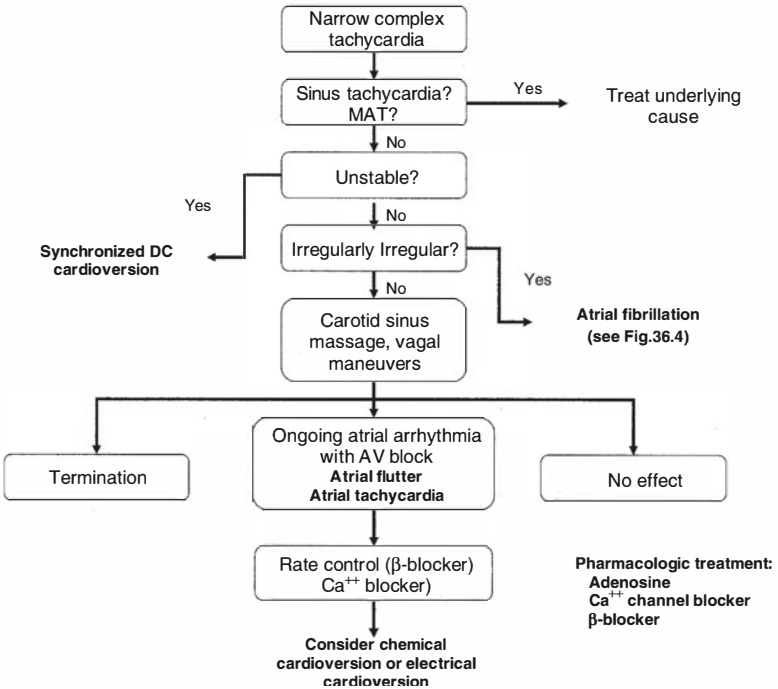

Figure 36-3. Therapeutic approach to narrow complex tachycardia.

V. SPECIFIC ARRHYTHMIAS AND THERAPIES

A. Atrial fibrillation.

1. Atrial fibrillation is the most common supraventricular tachycardia and has chaotic activation of the atria (Fig. 36-4F).
2. Acute treatment (Fig. 36-5).
   - **a.** Is the patient stable?
   - **b.** Unstable: Synchronized direct current cardioversion is the treatment of choice. Atrial fibrillation may be difficult to convert and require higher energies than other arrhythmias.
   - **c.** Stable: pharmacologic rate control.
     - **i.** β_1-Selective adrenergic receptor antagonists remain first-line therapy in nonasthmatic patients.
     - **ii.** Non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem).
     - **iii.** Digitalis may be used with relative safety in patients with poor ventricular function but provides only modest control of ventricular rate. It is ineffective in patients with high adrenergic tone or when very prompt rate control is required.

TABLE 36-1 Drugs for Supraventricular Tachycardias

Drug	Class	Dosage	Potential adverse effects
Adenosine		IV 6–12 mg bolus followed by saline flush	Transient chest pain, bronchoconstriction, complete heart block Potentiated by dipyridamole, heart transplant, and central administration route
Verapamil	IV	IV load 0.075–0.15 mg/kg over 5 min	Bradycardia, heart block, hypotension Edema, constipation
Diltiazem	IV	IV load 0.25 mg/kg over 2–5 min, then 5–15 mg/h maintenance PO 60–180 mg bid	Bradycardia, heart block, hypotension Edema, constipation
Metoprolol	II	IV load 2.5–5 mg q5 min upto 15 mg. May give IV maintenance 2.5–5 mg q6h PO 25–100 mg bid	Bronchoconstriction Bradycardia, heart block, hypotension
Propranolol	II	IV load 0.15 mg/kg PO maintenance 20–80 mg q6h	Bronchoconstriction Bradycardia, heart block, hypotension
Esmolol	II	IV 0.5 mg/kg over 1–2 min, then 0.05–0.2 mg/kg/min maintenance	Bronchoconstriction Bradycardia, heart block, hypotension
Procainamide	Ia	IV 15 mg/kg not faster than 50 mg/min	Hypotension, *torsades de pointes*, QT prolongation May slow atrial arrhythmia with faster ventricular response
Propafenone	Ic	PO 450–600 mg load; 150–300 mg q8h maintenance	Hypotension; may slow atrial arrhythmia with faster ventricular response, QRS prolongation
Flecainide	Ic	PO 200–300 mg load then 100–200 mg q12h	Ventricular arrhythmia; may slow atrial arrhythmia with faster ventricular response Hypotension
Sotalol	II/III	PO maintenance 80–160 mg bid	Bronchoconstriction; bradycardia; heart block; hypotension; QT prolongation; *torsades de pointes*

(Continued)

TABLE 36-1 Drugs for Supraventricular Tachycardias *(Continued)*

Drug	Class	Dosage	Potential adverse effects
Amiodarone	III	IV load 150 mg over 30–60 min then 950–1,200 mg IV daily IV or PO until 10 g administered, then 200–400 mg/d maintenance PO load 900–1,600 mg/d in three to four divided doses until 10 g administered then 200–400 mg daily maintenance. Reduce dosage if side effects. Try to use lowest effective maintenance dose.	Hypotension with rapid IV infusion; phlebitis if given peripherally. Toxicity to lungs, liver, skin, thyroid, and nerves and multiple other possible toxicities, including bradycardia and conduction defects. Monitor liver, lung, and thyroid function with chronic administration. Multiple potential drug interactions including digoxin and warfarin
Digoxin		IV 0.25 mg load q2–4h up to 1.5 mg; PO maintenance 0.125–0.25 mg daily	Bradycardia, heart block, atrial/ventricular tachycardia; interaction with multiple drugs
Dofetilide	III	PO dose according to creatinine clearance >60 mL/min—500 μg PO bid 40–60 mL/min—250 μg PO bid 20–40 mL/min—125 μg PO bid	QT prolongation; *torsades de pointes* Contraindicated if creatinine clearance <20 mL/min
Dronedarone	III	PO 400 mg BID	Contraindicated in heart failure and patients with persistent atrial fibrillation
Ibutilide	III	IV 1 mg over 10 min; may repeat 10 min after completion if necessary	QT prolongation; *torsades de pointes*

iv. Amiodarone effectively controls ventricular rate response during atrial fibrillation when administered IV and is relatively safe for use in patients with low ejection fraction. IV amiodarone should be administered through a central line to avoid phlebitis.

d. Treat underlying causes.

i. Stop offending drugs (e.g., methylxanthine derivatives).

ii. Correct electrolyte abnormalities.

iii. Attend to other cardiac, endocrine (particularly thyroid), and pulmonary disease.

iv. Correct/treat severe metabolic stress, severe noncardiac disease, and other hyperadrenergic states.

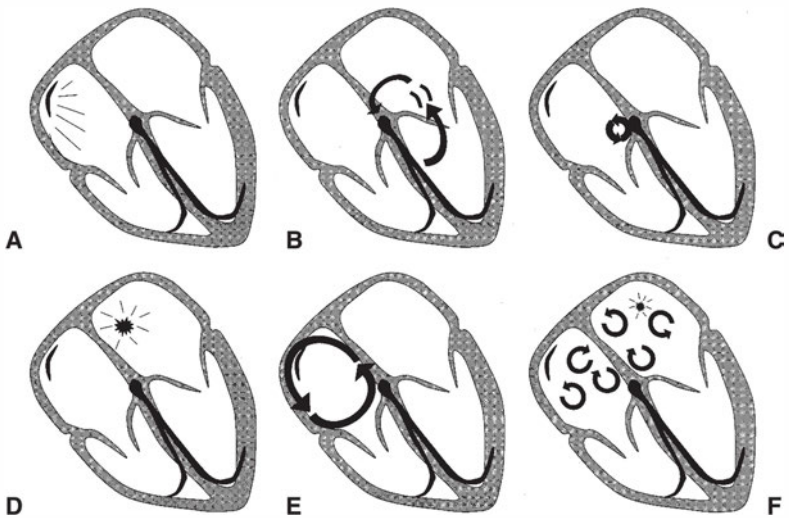

Figure 36-4. Mechanisms of supraventricular tachycardias. **A:** Inappropriate sinus tachycardia occurs when the sinus node or contiguous areas along the crista terminalis trigger heart rates that are inappropriately fast. **B:** AV reentry tachycardia uses an AP for retrograde conduction. APs may be manifest (WPW, pathway can conduct antegrade or retrograde, associated with delta wave on ECG) or concealed (incapable of antegrade conduction). Antegrade propagation via the His–Purkinje system leads to a narrow QRS, and reentry using the AP as the retrograde limb produces tachycardia. **C:** AV nodal reentry tachycardia utilizes two functional pathways within the AV node or approaches to the AV node, most commonly with antegrade conduction along the more slowly conducting pathway and retrograde conduction via the more rapidly conducting pathway. **D:** Ectopic atrial tachycardia requires the presence of a focus other than the sinus node, which usurps control of the atrial rate. The focus is often located on the crista terminalis, within a venous structure, or near an AV valve. **E:** Atrial flutter, in its most common (counter clockwise) form, consists of macroreentry within the right atrium. Activation proceeds up the interatrial septum, across the roof of the right atrium, anterolaterally anterior to the crista terminalis, and inferiorly to the Eustachian isthmus across, which it conducts back to the interatrial septum. The atrial rate is usually approximately 300 beats/min, with conduction to the ventricles limited by the AV node. **F:** Atrial fibrillation may be initiated by focal ectopy leading to multiple reentrant wavelets within the atria and a high-frequency barrage of impulses activating the AV node. Ventricular activation is limited by the AV node.

e. Rate versus rhythm control.

- **i.** Stable versus unstable patient.
- **ii.** Rate control and anticoagulation are a reasonable approach in stable patients with limited symptoms.
- **iii.** Patients in atrial fibrillation <48 hours or who have been anticoagulated (international normalized ratio >2 for at least 3 weeks) are candidates for early cardioversion.
- **iv.** Pharmacologic cardioversion: procainamide, flecainide, propafenone, dofetilide, ibutilide, and amiodarone. Class I drugs should always be preceded by rate control.

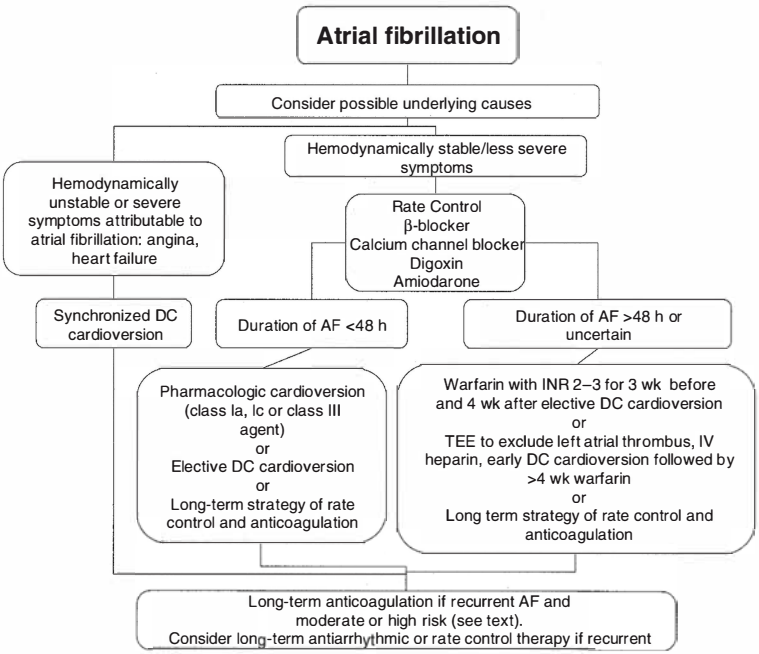

Figure 36-5. Therapeutic approach to atrial fibrillation.

v. Un- or inadequately anticoagulated patients in atrial fibrillation for more than 48 hours (or for an uncertain duration) are at elevated risk of thromboembolism. These patients require anticoagulation prior to conversion from atrial fibrillation. An alternative approach is to exclude left atrial thrombus with transesophageal echocardiography, to initiate IV anticoagulation, and to proceed to DC cardioversion, followed by oral anticoagulation for at least 4 weeks.

vi. Drug therapy to maintain sinus rhythm includes Class Ia, Ic, and III antiarrhythmic agents (see Table 36-1). This approach may be warranted in patients who do not tolerate or are symptomatic in atrial fibrillation.

vii. Catheter ablation of the AV node with permanent pacemaker implantation is particularly useful in patients with reduced left ventricular function and congestive heart failure in whom AV nodal blocking medications may be poorly tolerated or patients in whom rate control is difficult with conventional agents.

viii. Catheter ablation to treat atrial fibrillation (pulmonary vein isolation with or without additional atrial ablation) is an option for patients with symptomatic atrial fibrillation who have failed medical management. This approach is not usually a part of the acute management of atrial fibrillation.

f. Atrial fibrillation post–cardiac surgery. Atrial fibrillation is a common sequela to cardiac surgery, occurring in approximately 25% of patients.

i. Prophylactic treatment.

(a) Beta-blockade administered preoperatively is associated with a 77% reduction in relative risk of atrial fibrillation.

(b) Amiodarone administered orally preoperatively, or IV postoperatively, has been associated with reductions in the frequency of atrial fibrillation.

(c) Temporary atrial pacing post–cardiac surgery has also been associated with a decrease in the incidence of postoperative atrial fibrillation.

(d) In general, all patients undergoing cardiac surgery should receive prophylactic beta-blockade when not contraindicated. Those at especially high risk (older age, prior history of atrial fibrillation, mitral valve surgery) may be considered for prophylactic amiodarone therapy.

ii. Management of atrial fibrillation following cardiac surgery.

(a) Unstable patients require urgent cardioversion.

(b) Stable patients usually require rate control.

(c) Rate control and anticoagulation are appropriate for most patients; a large proportion of patients will convert spontaneously within a few months of surgery.

B. Atrial flutter.

1. Usually macroreentry with a single wavefront propagating counterclockwise around the tricuspid annulus, most commonly up the interatrial septum and down the right atrial free wall, anterior to the crista terminalis, and back across the isthmus between the inferior vena cava and tricuspid annulus (the cavotricuspid isthmus: CTI) (Fig. 36-4E).

2. ECG demonstrates typical flutter wave morphology, a slowly downsloping initial portion followed by a sharp upward deflection toward the baseline.

3. The clinical presentation and management of atrial flutter are very similar to those of atrial fibrillation. However, rate control can be more difficult to achieve, and radiofrequency ablation is more effective for atrial flutter.

4. Acute treatment.

a. Rate control, especially prior to attempting chemical cardioversion.

b. Typical atrial flutter is amenable to cure by catheter ablation. The narrow isthmus of atrium between the tricuspid annulus and inferior vena cava (CTI) can be interrupted by a line of ablation with a high success rate and few complications.

c. The risk of thromboembolism from atrial flutter is significant and is similar to atrial fibrillation. Atrial flutter warrants anticoagulation in the same manner as for atrial fibrillation.

C. AV nodal reentry tachycardia.

1. AVNRT is the most common cause of regular supraventricular tachycardia, accounting for up to 60% of cases.

2. Paroxysmal rapid regular narrow complex tachycardia with heart rate often 150 to 250 beats/min and P waves either buried within the QRS complex or visible at its termination (r' or S wave).
3. One of the causes of a "short RP tachycardia".
4. Symptoms: palpitations, pounding in the neck, lightheadedness, shortness of breath, chest pressure, weakness, and fatigue.
5. Presents most frequently in second to fifth decade, with a 70% female preponderance.
6. Initiated by a critically timed premature complex that blocks in the fast AV node pathway, conducts down the slow AV node pathway with a "jump" in the PR interval, and then reenters (Fig. 36-4C).
7. Atypical AVNRT is caused by reentry antegrade down the fast pathway and retrograde via the slow pathway. Usually a form of long RP tachycardia.
8. **Acute treatment**: See General Management of Supraventricular Tachycardias earlier.
9. **Chronic treatment.**
   a. Pharmacologic therapy: β-blockers, calcium channel blockers, occasionally digoxin, but rarely Class I and III agents.
   b. Catheter ablation is curative with low risk and no need for long-term drug therapy. Success is now over 95% with the major complication of heart block occurring in 0.5% to 1%.

D. AV reentry tachycardia.

1. AVRT is a common form of supraventricular tachycardia, accounting for up to 30% of patients.
2. During tachycardia, the QRS usually appears normal, and P waves, if visible, will be seen at the end of the QRS complex, within the ST segment, or within the T wave.
3. The mechanism of tachycardia is reentry; an AV accessory pathway (AP) is the retrograde limb, and the AV node is the antegrade limb (Fig. 36-4B).
4. APs are congenital anomalies of the heart that allow conduction of excitatory impulses, via muscle fibers, across the AV groove, bypassing the AV node.
5. **Acute treatment**: See General Management of Supraventricular Tachycardias earlier.
6. **Chronic treatment**: same as for AVNRT.

E. Wolff-Parkinson-White syndrome.

1. The Wolff-Parkinson-White syndrome (WPW) consists of a short PR interval and ventricular preexcitation (delta wave) due to an AP with symptoms of palpitations.
2. The most common arrhythmia associated with WPW is the regular, narrow complex tachycardia, AVRT.
3. A manifest AP is capable of antegrade conduction, often with a short refractory period. This bypasses the protective properties of the AV node, so that atrial tachycardia or atrial fibrillation may result in very fast ventricular rates, even inducing ventricular fibrillation.

4. Patients with WPW may be at risk for sudden cardiac death, although the overall risk is rather low, on the order of 0.15% per patient-year.
5. **Acute management.**
   a. Fast preexcited ventricular response to atrial fibrillation (irregular rhythm with varying wide QRS complexes) should undergo electrical cardioversion.
   b. Stable preexcited atrial fibrillation may be treated with Class Ia, Ic, or III drugs. IV ibutilide (1 to 2 mg IV) or procainamide (10 to 15 mg/kg IV).
   c. AV nodal blocking drugs should be avoided (digoxin, adenosine, calcium channel blockers, and β-blockers) because of the potential of increasing the ventricular rate due to increased AV nodal blockade and hypotension.
   d. Treatment of AVRT in patients with WPW: as above.
   e. **Chronic therapy.**
      i. Patients with symptoms or those in high-risk professions should undergo curative catheter ablation. Success and complication rates for catheter ablation of APs are dependent on pathway location. Generally success rates are >90% with a <2% complication rate.
      ii. Patients with a history of atrial fibrillation with rapid ventricular response or ventricular fibrillation should undergo catheter ablation.
      iii. Patients who are at low risk (intermittent preexcitation or sudden failure of preexcitation during increased atrial rates), yet who experience recurrent AVRT, may be treated similarly to patients with concealed APs or AV node reentry tachycardia.

F. Ectopic atrial tachycardia.

1. Ectopic atrial tachycardia most likely occurs as a result of abnormal automaticity or triggered activity within the atrium and may be more likely to be associated with structural heart disease than is AVNRT or AVRT.
2. Narrow complex tachycardia with an RP interval that is usually, but not always, longer than the PR interval, depending on AV nodal conduction properties.
3. The P-wave morphology may or may not be visibly different from sinus.
4. Ectopic atrial tachycardia may occur in short runs, may be sustained, or even may be incessant.
5. May be associated with underlying disease (coronary artery disease, myocardial infarction, ethanol ingestion, hypoxia, theophylline toxicity, digitalis toxicity, or electrolyte abnormalities).
6. **Acute treatment.**
   a. Beta-blockade.
   b. Calcium channel blockade.
   c. Class Ia and Ic antiarrhythmic drugs (with AV nodal blockade), amiodarone.
7. **Chronic treatment.**
   a. AV nodal blocking agents and antiarrhythmic agents, as above.
   b. Catheter ablation is a viable option for treatment of ectopic atrial tachycardia.

G. Multifocal atrial tachycardia.

1. Multifocal atrial tachycardia is uncommon, thought to be caused by abnormal automaticity or triggered activity and may be triggered by hypoxia, elevated sympathetic tone, hypokalemia, hypomagnesemia, or theophylline.
2. It is recognized by a rapid atrial rhythm with at least three P wave morphologies and variable ventricular response.
3. **Acute treatment.**
   - **a.** Beta-blockade: Caution is required in patients with reactive airways disease.
   - **b.** Calcium channel blockers may be effective and are the treatment of choice in patients with known reactive airways disease.
   - **c.** Underlying triggers must be addressed, including oxygenation, CO_2 clearance, magnesium and potassium repletion, and avoidance of methylxanthine derivatives (e.g., theophylline).

VI. CONCLUSIONS

Supraventricular tachycardias frequently complicate acute medical illness and uncommonly cause severe illness. An organized approach to patients presenting with these rhythms facilitates accurate diagnosis and thereby guides therapy. Most SVTs can be medically managed. However, DC cardioversion is a highly effective means of restoring sinus rhythm in unusual circumstances when more conservative measures fail. Atrial fibrillation is the most common SVT and can usually be managed with a combination of pharmacologic therapy, including anticoagulation, cardioversion, and treatment aimed at contributing causes.

SUGGESTED READINGS

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37 Temporary Cardiac Pacing

David D. Spragg and Daniel A. Kim

I. GENERAL PRINCIPLES

A. Background.

1. The purpose of temporary cardiac pacing is to reestablish circulatory integrity and normal hemodynamics in acutely compromised bradyarrhythmia or tachyarrhythmia by maintaining an appropriate heart rate until it resolves or until long-term therapy can be initiated.
2. Algorithm for managing patients with bradycardia (Fig. 37-1).

B. Pacing options.

1. Transcutaneous.
   a. Primary use: prophylaxis in patients at risk for high-grade atrioventricular (AV) block.
   b. Pros: multifunctional capabilities including sensing; can be used for overdrive pacing.
   c. Cons: patient discomfort, adequate ventricular capture may be challenging.
2. Transvenous: has commonly supplanted transcutaneous pacing given ease of use and less patient discomfort.

II. INDICATIONS

A. Overview.

1. Indications for temporary pacing in the setting of acute myocardial infarction (MI) have been well defined and outlined in a consensus guideline from American Heart Association and the American College of Cardiology (AHA/ACC) (see Table 37-1).
2. No similar guidelines available for other conditions causing bradycardia (i.e., electrolyte abnormalities, drug reactions, or infections).
3. Of patients needing temporary pacing, about half require permanent pacing before discharge.

B. Specific indications.

1. MI (Table 37-1).
   a. Bradycardia/AV block related to ischemia or infarction of conduction system.
      i. Revascularization is the primary management—in particular when AV nodal or fascicular blood supply is compromised.

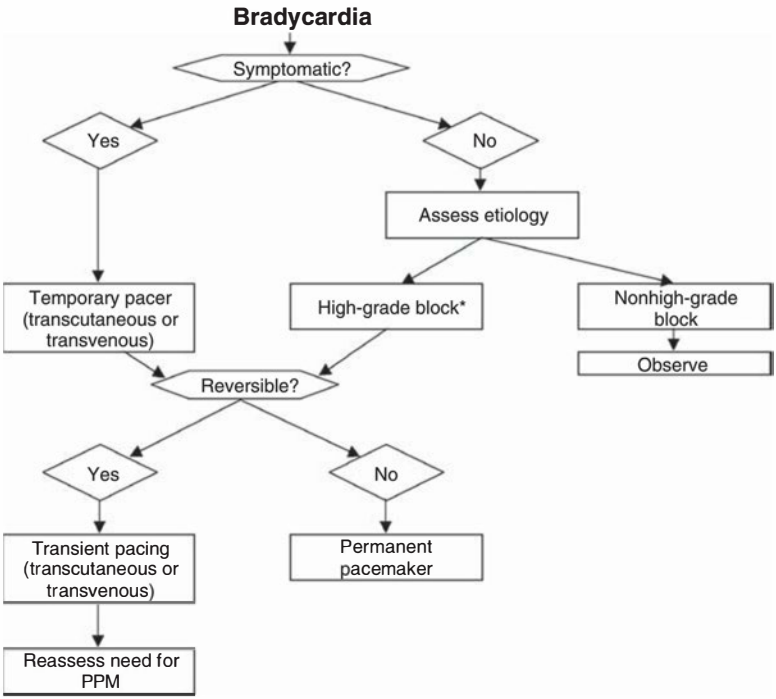

Figure 37-1. Algorithm for management of bradycardia unresponsive to pharmacologic therapy. *High-grade block includes the Class I indications on Table 37-1. PPM, permanent pacemaker.

(a) Inferior ischemia (disruption of AV nodal blood supply).
(b) Anterior ischemia (disruption of fascicular blood supply).

ii. Prognosis.
(a) Depends on extent of underlying ischemia and LV function.
(b) Death is rare from complete heart block.

2. Bradyarrhythmias (Table 37-2: Section I).
a. The most common indication is symptomatic bradycardia that is unresponsive to pharmacologic therapy.
b. Classifications.
i. Disordered impulse formation (i.e., sinus node dysfunction).
ii. Disordered impulse propagation (i.e., conduction block).

3. Tachyarrhythmias (Table 37-2: Section II).
a. Temporary pacing rarely used in clinical practice due to efficacy of medications and increased prevalence of implantable defibrillators.
b. Pacing can play a role in prevention or termination of arrhythmia.
c. Many reentrant rhythms are susceptible to pace termination.
i. Supraventricular tachycardia (SVT) (AV nodal reentrant tachycardia, accessory pathway–mediated tachycardia).
ii. Ventricular tachycardia (VT) (scar mediated).

TABLE 37-1 Indications of Pacing in Acute Myocardial Infarction

Placement of transcutaneous patches and active (demand) transcutaneous pacing	
Class I	Sinus bradycardia (<50 bpm) with systolic BP < 80 mm Hg unresponsive to drug therapy
	Mobitz type II second-degree AV block
	Third-degree heart block
	BBBB (alternative RBBB and LBBB)
	Newly acquired or age-indeterminate LBBB, RBBB and LAFB, or RBBB and LPFB
	RBBB or LBBB with first-degree AV block
Class IIa	Stable bradycardia with systolic BP > 90 mm Hg or hemodynamic compromise responsive to drug therapy
	Newly acquired or age-indeterminate RBBB
Class IIb	Newly acquired or age-indeterminate first-degree AV block
Class III	Uncomplicated acute MI without evidence of conduction system disease
Temporary transvenous pacing	
Class I	Asystole
	Symptomatic bradycardia
	Sinus bradycardia with hypotension
	Type I second-degree AV block with hypotension unresponsive to atropine
	Mobitz type II second-degree AV block
	BBBB (alternating BBB or RBBB with alternating LAFB/LPFB) of any age
	New or indeterminate-age bifascicular block (RBBB with LAFB or LPFB or LBBB) with first-degree AV block
Class IIa	Recurrent sinus pauses (>3 s) not responsive to atropine
	RBBB with first-degree AV block
	New or age-indeterminate RBBB and LAFB or LPFB
	New or age-indeterminate LBBB
	Incessant VT for atrial or ventricular overdrive pacing
Class IIb	Bifascicular block of indeterminate age
	New or age-indeterminate isolated RBBB
Class III	First-degree heart block
	Type I second-degree AV block (Wenckebach) with normal hemodynamics
	Accelerated idioventricular rhythm
	BBB or fascicular block known to exist before acute MI

BP, blood pressure; BBBB, bilateral bundle branch block; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; AV, atrioventricular; MI, myocardial infarction; BBB, bundle branch block.
Adapted from ACC/AHA guidelines for the management of patients with ST-Elevation myocardial infarction: executive summary. *J Am Coll Cardiol* 2004;3:671–719.

TABLE 37-2 Indications for Transvenous Pacing in the Absence of Myocardial Ischemia

I. Bradyarrhythmias
Prolonged sinus pauses (>3 s)
Symptomatic sinus bradycardia
Symptomatic second- or third-degree AV block
Complete heart block secondary to structural heart disease
Asystole
Alternating bundle branch block

II. Tachyarrhythmias
Symptomatic
Sustained pause-dependent VT
Torsade de pointes associated with structural heart disease, metabolic abnormalities, or drug effects
SVT or VT unresponsive to medical therapy

III. Prophylaxis for procedures or conditions, which may promote bradycardia
General anesthesia with concomitant conduction block
Intermittent or sustained second- or third-degree AV block
First-degree AV block with bifascicular block or LBBB
Cardiac surgery
Tricuspid valve surgery
Ventricular septal defect closure
Ostium primum repair
Surgical procedures requiring permanent pacemaker deactivation
Percutaneous coronary intervention with associated bradycardia
Right heart catheterization or endocardial biopsy in a patient with associated LBBB
Cardioversion with sick sinus syndrome
New AV block or bundle branch block with endocarditis before cardiac surgery
Lyme carditis with associated conduction block
Electrophysiology studies
To allow pharmacologic treatment with drugs that worsens bradycardia

VT, ventricular tachycardia; SVT, supraventricular tachycardia; AV, atrioventricular; LBBB, left bundle branch block.

d. Prevention of triggered arrhythmia (i.e., torsade de pointes).
i. Shortening of QT interval with pacing to reduce risk of polymorphic VT.
e. No role in management of ventricular fibrillation (VF) or triggered VT.

4. Prophylaxis (Table 37-2: Section III).

C. Contraindications.

1. Asystolic arrest victims: no survival benefit from temporary pacing.
2. Risks outweigh benefits: that is, in a patient with a MI who received a thrombolytic agent and being aggressively treated with antiplatelet/anticoagulation agents.

3. Asymptomatic patient with stable escape rhythm (may become pacing dependent).
4. Bradyarrhythmia secondary to profound hypothermia.
5. Relative contraindication if it is not possible to achieve right ventricle (RV) capture: that is, prosthetic tricuspid valve or RV infarct.

III. PROCEDURE

A. Equipment.

1. Transcutaneous.
   a. External electrode pads.
   b. External pulse generator.
2. Transvenous.
   a. Central venous access kit.
   b. Balloon-tipped electrode catheter.
   c. External pulse generator, power source.

B. Technique.

1. Transcutaneous.
   a. Electrode placement: anteroposterior or anterolateral.
   b. Pacing threshold: lowest amount of current necessary to depolarize the ventricles.
      i. Output ranges 0 to 140 mA.
      ii. Output increased until a pacer stimulus captures.
      iii. Threshold is determined: typically 40 to 70 mA in healthy individuals.
      iv. Higher outputs improve capture, but associated with discomfort and skin injury.
      v. Factors that increase threshold: poor skin-to-electrode contact, obesity, myocardial ischemia, metabolic derangement, pneumothorax, communication equipment (cell phones).
   c. Pacing rate: based on clinical scenario for protection of symptomatic bradycardia.
      i. Usually 40 to 50 bpm as backup to intrinsic rate unless cardiac output is very low.
      ii. Approximately 100 bpm for tachyarrhythmia prevention until underlying process corrected.
2. Transvenous.
   a. Each site has limitations: internal jugular, subclavian, brachial, or femoral veins.
      i. The best approach is the site most comfortable for the individual placing the device.
      ii. Access via right internal jugular vein in general has the highest success and fewest complications.
      iii. Left subclavian should be avoided if anticipated need for permanent pacer.
      iv. Femoral: increased risk of deep vein thrombosis and infection and decreased mobility.
      v. Brachial: increased risk of cardiac puncture and instability.

b. Guidance.
  i. Fluoroscopy is helpful in positioning, but not necessary.
  ii. If no fluoroscopy available, use balloon-tipped catheter with electrogram.
c. Electrode catheter placement (Table 37-3).
d. Pacing mode.
  i. Synchronous or asynchronous (fixed).
  ii. Ventricular demand pacemaker (VVI): the most commonly used mode to manage bradycardia.
  iii. Biventricular (via coronary sinus): may provide short-term benefit to selected patients in cardiogenic shock. Response to this therapy may help to stabilize a patient and determine benefit of a permanent biventricular device.

TABLE 37-3 Placement of a Temporary Electrode Catheter

Setup
Sterile preparations: gown, gloves, mask, hat, drape
Equipment: pacing electrode catheter, pulse generator, surface electrodes, sheath
Connections
  Proximal electrode catheter connects to positive pole of pulse generator.
  Distal electrode connects to V1 surface electrode.

Testing components
Inflate balloon to test integrity.
Document V1 recordings when inserting electrode catheter into the sheath.

Procedure
Carefully advance electrode catheter 15 cm and inflate balloon.
Observe V1 transition with advancement of catheter.
  Atrial (P wave) dominant
  Ventricular (QRS) dominant
  Injury current
Stop advancing once injury current is detected.

Pacing preparation
Confirm proximal electrode is connected to positive pole of pulse generator.
Disconnect distal electrode from V1 surface lead.
Connect distal electrode to the negative pole of the pulse generator.

Pacing
Attempt pacing at 10 mA with the highest sensitivity.
Observe capture.
Determine thresholds and set out 1–2 mA above threshold (generally 3 mA).

Postprocedure
Document distance electrode is within the sheath.
Confirm position with ECG and chest radiograph.
Routine care of pacemaker and site
  Pacing parameters: threshold, rate, sensitivity, output
  Skin site: observing for infection

C. Efficacy.

1. Transcutaneous.
   a. Safe and effective.
   b. Primary limitation is patient discomfort, which may improve with sedation.
   c. Similar achievable hemodynamic response compared with transvenous pacing (both in measured cardiac output and blood pressure augmentation).
2. Transvenous.
   a. High procedural success.
   b. Offers a low output with minimal discomfort (no skeletal muscle pacing).

IV. POSTPROCEDURE CONSIDERATIONS

A. Complications (Table 37-4).

1. Transcutaneous.
   a. Local discomfort: temporary erythema at contact site of the electrodes, tingling, pain.

TABLE 37-4 Troubleshooting

Capture
Loss of capture
  Loose connections
Electrode catheter malposition
  Lead fracture
  Increased myocardial stimulation threshold
  Cardiac penetration or perforation
  Pulse generator malfunction or battery depletion
Insufficient voltage to pace the ventricle

Sensing
Loss of sensing
  Lead malposition or fracture
  Inadequate intracardiac signal
  Increase threshold
Hypoxia, acidosis, Class I antiarrhythmic drugs, electrolytes abnormalities
Area of lead contact may exhibit inflammation and fibrosis.
  Spontaneous complexes falling within refractory period of generator
  Generator malfunction or battery depletion
Undersensing intracardiac signals
Oversensing
  P wave
  T wave
  Myopotentials
  Electromagnetic interference
  False signals generated from extension cables

b. Skin injury limited due to improved electrode pads: burns.
c. Malpositioning causes excessive skeletal muscle contraction and increased output requirements.
d. Failure to capture.

2. Transvenous.
a. Low risk, complication rate 13% to 18%.
i. Sequelae of venous access: pneumothorax, hemothorax, infection, thromboembolism, bleeding, air embolism, or nerve damage.
ii. Arrhythmia: SVT, VT, Vfib.
iii. Myocardial perforation, pericarditis, tamponade.
b. Component malfunction is rare.
c. Diaphragmatic pacing: Beware of patient hiccupping at a rate identical to pacer rate.
i. May indicate RV wall perforation or high preset voltage.

B. Monitoring.

1. Intensive care setting monitoring needed while a temporary pacing system is in place.
2. Pacing and sensing should be assessed daily, including measurements of threshold.
3. Observe for signs of infection.

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38 Permanent Pacemakers and Antiarrhythmic Devices

Anil Rajendra and Michael R. Gold

I. PERMANENT PACEMAKERS (PPMS)

A. General principles.

1. Pacemaker nomenclature (Table 38-1).
2. Current pacemaker designs.
   - a. Single chamber (SC): lead in only one chamber, usually the right ventricle (RV).
     - i. Used primarily in patients with chronic atrial fibrillation (AF).
   - b. Dual chamber (DC): leads in both the right atrium (RA) and RV.
     - i. Able to mimic normal cardiac physiology with sequential atrial to ventricular (A–V) pacing and have less AF than RV-only devices. However, frequent RV pacing is associated with heart failure and worsening left ventricular (LV) function.
   - c. Biventricular (BiV) devices: leads in the RV and LV, as well as typically the RA.
     - i. Simultaneously or sequentially pace the RV and LV.

B. Indications.

1. Dual chamber (DC).
   - a. Symptomatic bradycardia.
   - b. Profound bradycardia without symptoms.
   - c. Conduction system disease with high risk of progression to life-threatening bradycardia.
   - d. Pause-dependent ventricular tachycardia (VT).
2. Cardiac resynchronization therapy (CRT): BiV pacing (Table 38-2).
   - a. Reduces mortality/hospitalization in heart failure patients with reduced ejection fraction and prolonged QRS duration (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION], Cardiac Resynchronization Heart Failure [CARE-HF], Resynchronization/Defibrillation in Ambulatory Heart Failure [RAFT]).
   - b. Most trials, including Multicenter InSync Randomized Clinical Evaluation (MIRACLE), showed improved QOL, exercise tolerance, and reversal of remodeling with CRT.
   - c. Cardiovascular benefits may be attenuated in the setting of AF.
     - i. Patients with chronic AF failed to show improvement with CRT in mortality, QOL questionnaire, or 6-minute walk test (RAFT trial). This may be due to less consistent pacing in AF.

TABLE 38-1 Pacemaker Nomenclature Codes

First letter = chamber(s) paced: A, V, or D
Second letter = chamber(s) sensed: A, V, or D
Third letter = what the device does with the sensed information: O, I, or D
Fourth = rate responsiveness: O or R
Examples
- VOO
- VVI
- AAI
- DDD
- DDDR

CRT = pacing in both ventricles, aka BiV pacing
CRT-P: device with pacing-only function
CRT-D: device with BiV pacing and ICD capabilities

V, ventricle; A, atrial; D, dual (A and V, or pace and inhibit); I, inhibit; R, rate responsiveness; O, does nothing; VOO, ventricular asynchronous; VVI, ventricular inhibited; AAI, atrial inhibited; DDD, dual-chamber pacing and sensing, both triggered and inhibited mode; DDDR, AV concordance with physiologic response; CRT, cardiac resynchronization therapy; BiV, biventricular; ICD, implantable cardioverter–defibrillator.

TABLE 38-2 Indications for Cardiac Resynchronization Therapy[a]

Class I
- EF < 35%, sinus rhythm, QRS duration >150 ms, NYHA Class II, III, or ambulatory IV

Class IIa
- EF < 35%, sinus rhythm, LBBB with QRS duration 120–149 ms, NYHA Class II, III, ambulatory Class IV
- EF < 35%, sinus rhythm, non-LBBB with QRS duration >150 ms, NYHA III or ambulatory Class IV
- EF < 35%, undergoing device replacement and anticipated significant (>40%) ventricular pacing
- EF < 35%, AF, if
  a) Requires ventricular pacing or otherwise meets CRT criteria
  b) AV nodal ablation or rate control will allow near 100% biventricular pacing.

[a]Patients must be on guideline-directed medical therapy (GDMT), including beta-blocker and ACE inhibitor or ARB.
CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; LBBB, left bundle branch block; AF, atrial fibrillation.

C. Procedure.

1. Placed percutaneously through the subclavian/axillary vein, with pulse generator implanted in subcutaneous pocket superficial to prepectoral fascia.
2. Strict sterile technique observed to prevent infection.
3. Leads placed in RA and RV apex/interventricular septum.
4. CRT: LV lead placed on the LV lateral wall via the coronary sinus branches avoiding the apical region.

D. Postprocedure considerations.

1. Complications.
   - a. Immediate.
     - i. Pneumothorax/hemothorax.
     - ii. Pocket hematoma: higher incidence in patients on heparin products versus warfarin.
     - iii. Pocket and/or lead infection.
   - b. Immediate to chronic.
     - i. Lead fracture/malfunction: x-ray usually may detect; presents as loss of capture and increased impedance—occurs at point of mechanical stress.
     - ii. Lead insulation break: invisible on x-ray; presents as oversensing (inappropriate inhibition) and decreased impedance.
     - iii. Electromagnetic interference: Electrocautery in surgical procedures causes inhibition; set device to nonsensing mode, for example, VOO and DOO, if pacemaker dependent; can be done through reprogramming or with magnet overlying device.
     - iv. Pacemaker infection: most serious when bacteremia is present and often requires removal of pulse generator and leads.
     - v. Pacemaker syndrome: hypotension and palpitations from loss of synchronized atrial–ventricular systole resulting in atrial contraction against closed atrioventricular (AV) valves; occurs primarily during intermittent VVI pacing; hallmark on physical exam is a "cannon A wave." May be managed by upgrading to a dual-chamber pacing system or by adjustment of pacing parameters to optimize AV synchrony.
     - vi. Upper rate-limit pacing: with rapid intrinsic atrial rates, for example, atrial flutter, multifocal atrial tachycardia (MAT), pacemaker tracks fast atrial rate, paces at same fast rate in ventricle(s); nontracking modes (e.g., DDI) or mode switching to nontracking mode when atrial rate exceeds set upper rate limit prevents this problem.
     - vii. Pacemaker-mediated tachycardia (PMT): ventricle(s) paced → retrograde impulse to atria → atrial contraction from retrograde signal → sensed by the atrial lead → sensed atrial impulse tracked → second ventricular output created → second impulse goes retrograde to atria → cycle repeats; special algorithms to interrupt upper limit tracking and prevent PMT.
     - viii. Device erosion: occurs at point of skin tension, especially in thin patients and associated with infection and "twiddler's syndrome" (habitual manipulation of device by patient).

2. Monitoring.
   a. Immediate.
      i. Chest radiography (chest x-ray [CXR]; two views) after implantation to confirm lead placement and rule out other complications.
      ii. Programming to individualize/optimize therapy, minimize right ventricular pacing in SC and DC devices, maximize biventricular pacing in CRT devices.
   b. Immediate to chronic.
      i. Pacemaker parameters routinely interrogated after implantation and at follow-up (typically 2 to 6 weeks after implant, then every 6 to 12 months).
      ii. Battery depletion: Expected life is 6 to 10 years but varies depending on device type, number of leads, amount of pacing, lead impedance, and pacing thresholds.
   c. Programming.
      i. For DC PPM, important to minimize RV pacing → reduces incidence of AF and congestive heart failure (CHF). Achieved by extending AV delay.
      ii. For CRT, to insure near 100% biventricular pacing.

II. IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

A. General principles.

1. Defibrillation threshold (DFT): minimal energy required for defibrillation. The routine assessment of DFT at implantation is controversial.
2. Sensing: ability to detect ventricular fibrillation (VF) and VT, but avoid inappropriate shocks for supraventricular arrhythmias (see below, Section II.D.2.b).
3. All current transvenous implantable cardioverter–defibrillators (ICDs) have PPM capabilities (VVI, DC, or BiV).
4. Subcutaneous ICDs (S-ICD) avoid transvenous leads but only have postshock pacing capabilities.
5. Defibrillation: application of electrical shock to tachycardia to reset action potential and restore sinus rhythm.
6. Antitachycardia pacing (ATP): pacing faster than arrhythmia to overdrive and terminate.

B. Indications.

1. Primary prevention.
   a. Cardiomyopathies (Table 38-3).
   b. Clinical scenarios: syncope with clinically relevant sustained VT or VF on electrophysiology study (EPS).
2. Secondary prevention (previous history of VT or VF): Multiple prospective trials demonstrate robust and reproducible effect of improved survival compared with drug therapy (Antiarrhythmics vs. Implantable Defibrillators [AVID], Cardiac Arrest Study Hamburg [CASH], Canadian Implantable Defibrillator Study [CIDS]).

TABLE 38-3 Ejection Fraction Requirements for ICD Implantation by Cardiomyopathy Type[a]

Ischemic	
Current guideline requirements for ICD	**Source trial(s)**
EF < 35%, NYHA II–III	SCD-HeFT, MADIT-II
EF < 30%, NYHA I	MADIT-II
EF < 40%, NSVT and inducible VF or sustained VT at EPS	MADIT, MUSTT
Nonischemic	
Clinical requirement	**Source trial**
EF ≤ 35%, NYHA II–III	SCD-HeFT

[a]EF on β-blocker and ACE inhibitor/angiotensin II receptor blocker (ARB) ≥6 wk and patient must be at least 40 d post-MI unless positive EPS.
ICD, implantable cardioverter–defibrillator; EF, ejection fraction; NYHA, New York Heart Association; SCD, sudden cardiac death; HeFT, Heart Failure Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; NSVT, nonsustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; EPS, electrophysiologic study; MUSTT, Multicenter Unsustained Tachycardia Trial.

C. Procedure.

1. Similar to PPM implantation except for S-ICD where the lead is placed in the parasternal subcutaneous space with a left flank pulse generator.
2. If patient has a PPM, can upgrade to PPM/ICD or BiV/ICD in original pocket. Complication rates are higher with upgrade procedures.

D. Postprocedure considerations.

1. Programming: The following are adjustable.
   - **a.** Ventricular rate threshold over, which VT should be paced or shocked (VT zone).
   - **b.** Number of ATP trains (attempts) before defibrillation attempted.
   - **c.** Tiered therapy: ATP, then varied energy of shocks.
   - **d.** Therapies off if patient made comfort care only or transiently during a surgical procedure.
2. Complications.
   - **a.** Immediate: similar to pacemaker complications.
   - **b.** Intermediate to long term: similar to PPM with additional concern of oversensing (may lead to inappropriate therapy shocks/ATP). Potential causes of over sensing.
     - **i.** RV pacing always bipolar in ICDs (minimizes oversensing).
     - **ii.** Supraventricular tachycardia (SVT)/AF is a frequent cause of inappropriate shocks.
     - **iii.** Prominent T waves can lead to double counting.

iv. Lead insulation break (increased levels of "noise").
v. Pacemaker artifacts.
vi. Myopotentials, especially diaphragmatic.
vii. Electromagnetic interference (e.g., electrocautery, electronic surveillance devices, cellular telephones).

c. Magnetic resonance imaging (MRI) and PPM/ICD.
i. Damage to lead/myocardial interface possible, increased DFT, and impedance. MRI compatible pacemakers are now available.

3. Maintenance.
a. Defibrillation testing at implantation is now controversial and not routinely performed.
i. Antiarrhythmic drug initiation (especially amiodarone): DFT testing recommended 4 to 6 weeks after starting drug.
ii. Defibrillation testing should be avoided in the presence of hemodynamic instability or AF and inadequate anticoagulation.
b. Pulse generator changes every 5 to 9 years.

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SECTION 4

Pulmonary Problems in the Intensive Care Unit

J. Mark Madison

39

A Physiological Approach to Managing Respiratory Failure

Mark M. Wilson and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Respiratory failure is defined simplistically by arterial carbon dioxide tension ($Paco_2$) > 50 mm Hg or a sea level arterial oxygen tension (Pao_2) < 50 to 60 mm Hg.

B. The efficiency of gas exchange is evaluated by measuring the Pao_2, the $Paco_2$, and the alveolar–arterial (A–a) Po_2 gradient on room air or the Pao_2/Fio_2 (fraction of inspired oxygen) ratio for patients on high Fio_2.

1. **Pao_2:** The normal value for Pao_2 depends on the age and body position of the patient.

$$\text{In the upright position, } Pao_2 = 104.2 - 0.27 \times \text{age (years)}$$
$$\text{In the supine position, } Pao_2 = 103.5 - 0.47 \times \text{age (years)}$$

2. **$Paco_2$:** The normal $Paco_2$ is 35 to 45 mm Hg and is unaffected by age or body position. Because CO_2 production does not vary widely even in critically ill patients, it can be generally assumed that $Paco_2$ will vary inversely with alveolar ventilation.

3. **P_{AO_2}–P_{aO_2} gradient:** To help interpret a decrease in P_{aO_2}, one must know the A–a gradient. The alveolar P_{O_2} (P_{AO_2}) can be calculated from the simplified alveolar air equation.

$$P_{AO_2} = P_{IO_2} - P_{aCO_2}/R$$

At sea level and breathing room air, the P_{IO_2}, the partial pressure of inspired O_2, can be assumed to be 150 mm Hg. R is the respiratory exchange ratio and is assumed to be 0.8.
After subtracting P_{aO_2}, the normal A–a gradient is 5 (in a 20-year-old) to 10 (in a 35-year-old) mm Hg and is a sensitive indicator of intrinsic lung disease. At any age, an A–a gradient exceeding 20 mm Hg should be considered abnormal. With an F_{IO_2} above 0.21, the A–a gradient becomes a less accurate measure of gas exchange efficiency.

4. **P_{aO_2}/F_{IO_2} ratio:** used to estimate the severity of a gas exchange defect with patients receiving supplemental O_2. F_{IO_2} is expressed as a decimal. Values between 200 and 299 indicate moderate impairment with gas exchange (e.g., acute lung injury); values <200 indicate severe impairment (e.g., acute respiratory distress syndrome).

II. PATHOPHYSIOLOGY

A. Hypoxemia.

1. Five mechanisms can cause hypoxemia: low P_{IO_2}, hypoventilation, low ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch, right-to-left shunting, and diffusion impairment.
2. A low P_{IO_2} is generally seen only at high altitude.
3. Diffusion impairment alone is not the major cause of hypoxemia.
4. In the clinical setting, hypoventilation, low $\dot{V}/\dot{Q}$ mismatch, and right-to-left shunting or combinations of these are essentially the only important pathophysiologic causes of hypoxemia.
5. Hypoventilation, a decrease in alveolar ventilation for a given metabolic demand, results from a decrease in minute ventilation from extrapulmonary dysfunction. With no underlying abnormality of gas exchange, the A–a gradient, measured on room air, remains normal.
6. In areas of inadequate ventilation for a given level of perfusion (low $\dot{V}/\dot{Q}$ mismatch), pulmonary venous blood has a relative decrease in both P_{O_2} and percentage of oxyhemoglobin saturation. The result is a decreased P_{aO_2} and increased A–a gradient.
7. Right-to-left shunting refers to mixed venous blood going directly into the arterial circulation without having first been exposed to alveolar gas (from cardiac or great vessel, pulmonary vascular, or pulmonary parenchymal conditions). When the shunted blood mixes with the rest of the arterial blood, it lowers the average O_2 content and therefore the average P_{aO_2}. The A–a gradient is always increased.

B. Hypercapnia.

1. Three mechanisms can lead to an elevated P_{aCO_2}: breathing a gas containing CO_2, hypoventilation, and severe low $\dot{V}/\dot{Q}$ mismatch. Clinically, only the last two are important. Hypoventilation has already

been discussed. In patients who cannot augment their alveolar ventilation (e.g., severe chronic obstructive pulmonary disease [COPD] with chronic hypercapnia), hypercapnia can worsen with fever or overfeeding because of an increase in tissue CO_2 production coupled with an impaired capacity to eliminate CO_2.

2. The major mechanism causing arterial hypercapnia in patients with severe intrinsic lung disease is severe low $\dot{V}/\dot{Q}$ mismatch. A substantially greater degree of low $\dot{V}/\dot{Q}$ mismatch must be present to cause arterial hypercapnia than hypoxemia.
3. Although not a primary cause of hypercapnia, respiratory muscle overload (from increased work of breathing associated with severe lung derangement or fatigue) may result in relative hypoventilation because of the inability to increase minute ventilation appropriately.

C. Respiratory acid–base disorders.

1. Acid–base balance is assessed clinically from the arterial hydrogen ion (H^+) concentration. The ratio of the relative availability of acid versus base determines the H^+ concentration, as shown by the Henderson version of the Henderson-Hasselbalch equation.

$$H^+ = 24 \times (Paco_2 / HCO_3^-)$$

A pH of 7.40 corresponds to an H^+ concentration of 40 nanoequivalents/L, and each change in pH of 0.01 units corresponds to an opposite deviation in H^+ concentration of 1 nanoequivalent/L when the pH is 7.28 to 7.45. Outside this range, it is still clinically useful to estimate the H^+ concentration in this manner because the estimated value will deviate from the true value by no more than 5% to 10%.

2. In primary respiratory acidosis, the $Paco_2$ is elevated because of respiratory system dysfunction. Under normal circumstances, an appropriate compensatory change (i.e., increase) will occur in the HCO_3^- level to help mitigate the effect on H^+ concentration. To estimate how long the $Paco_2$ has been elevated, the ratio of $\Delta H^+/\Delta Paco_2$ is computed. The kidneys gradually increase the HCO_3^- level to bring H^+ concentration back toward, but not to, normal. The $\Delta H^+/\Delta Paco_2$ ratios for acute and chronic respiratory acidosis are 0.8 and 0.3, respectively. When previous blood gas values are not available, assume the change in $Paco_2$ occurred from 40 mm Hg and pH from 7.40 or H^+ 40 nanoequivalents.
3. The differential diagnosis of respiratory acidosis is the same as that of hypercapnic respiratory failure (Table 39-1). The therapeutic approach is also the same.
4. Primary respiratory alkalosis is defined by a decrease in $Paco_2$ with an accompanying compensatory decrease in HCO_3^-. The duration of respiratory alkalosis involves the same determination of $\Delta H^+/\Delta Paco_2$ ratios. The values for acute and chronic respiratory alkalosis are 0.8 and 0.17, respectively. A primary respiratory alkalosis may have a normal or an elevated (A–a) Po_2 gradient. The differential diagnosis of respiratory alkalosis with an elevated (A–a) Po_2 gradient is the same as that of hypoxemic respiratory failure (e.g., acute asthma, pneumonia, pulmonary embolism, pulmonary edema). The differential diagnosis of respiratory

TABLE 39-1 Causes of Hypercapnia and Their Pathophysiologic Mechanisms[a]

Site of abnormality	Disease	Mechanism
Pulmonary disorders of		Severe ventilation–perfusion mismatch
Lower airways	COPD, asthma, cystic fibrosis	
Lung parenchyma	Environmental/occupational lung disease	
Pulmonary vasculature	Pulmonary embolism (rarely)[b]	
Extrapulmonary disorders of		Hypoventilation
Central nervous system	Respiratory center depression due to drug overdose, primary alveolar hypoventilation, myxedema	
Peripheral nervous system	Spinal cord disease, amyotrophic lateral sclerosis, Guillain-Barré syndrome	
Respiratory muscles	Myasthenia gravis, polymyositis, severe hypophosphatemia	
Chest wall	Ankylosing spondylitis, flail chest, thoracoplasty	
Pleura	Restrictive pleuritis	
Upper airways	Tracheal obstruction, epiglottitis, adenoidal and tonsillar hypertrophy, obstructive sleep apnea	

[a]This table is not an exhaustive listing; it includes the more common causes for each involved compartment of the respiratory system.
[b]Because the drive to breathe is increased with pulmonary embolism, hypercapnia generally only occurs when the patient is unable to increase minute ventilation (e.g., patient with pulmonary embolism on controlled mechanical ventilation).

alkalosis with a normal (A–a) P_{O_2} gradient includes central nervous system disorders, pregnancy, high altitude, severe anemia, hyperventilation, hepatic failure, and catecholamine, progesterone, or thyroid hormone excess. The combination of an elevated anion-gap metabolic acidosis with an "overcompensated" respiratory alkalosis should alert the clinician to evaluate for salicylate intoxication.

III. DIAGNOSIS

A. To determine the cause of hypoxemia, one must evaluate the P_{ACO_2}, the (A–a) P_{O_2} gradient, and occasionally the patient's response to 100% O_2.

B. During hypoventilation, the P_{ACO_2} is always elevated, the (A–a) P_{O_2} gradient is normal (20 mm Hg or less), and the decrease in P_{AO_2} is accounted for solely by the low P_{AO_2}. If the patient is given 100% O_2 to breathe (rarely necessary), there will be a dramatic increase in P_{AO_2} (to more than 500 mm Hg).

C. During $\dot{V}/\dot{Q}$ mismatch and right-to-left shunting, the decreased P_{AO_2} is typically accompanied by an elevated (A–a) P_{O_2} gradient. During $\dot{V}/\dot{Q}$ mismatch, the P_{ACO_2} may or may not be elevated, whereas it is rarely elevated in right-to-left shunt. The P_{AO_2} in the patient with $\dot{V}/\dot{Q}$ mismatch shows a dramatic rise in response to 100% O_2 (to more than 500 mm Hg). The patient with right-to-left shunting shows minimal or, in severe cases, no response at all to 100% O_2.

D. Contrast echocardiography or quantitative nuclear medicine perfusion lung/brain/kidney scanning can be obtained to differentiate the right-to-left shunt of cardiac, great vessel, or pulmonary vascular origin from a pulmonary parenchymal cause. By echocardiography, with cardiac, great vessel, or pulmonary vascular shunting, there will be too rapid a transit of contrast from the venous circulation into the left side of the heart and systemic arterial circulation indicative of a structural/anatomic defect. By nuclear medicine scanning, the percent of right-to-left nonpulmonary parenchymal shunt can be calculated by determining the percentage of counts that appear in the brain and kidneys.

E. With hypercapnic respiratory failure (Table 39-1), the (A–a) P_{O_2} gradient may or may not be increased. Commonly, a disease process may affect oxygenation or ventilation through a combination of the mechanisms described earlier. See Chapter 43 for discussion of extrapulmonary causes of respiratory failure.

IV. TREATMENT

A. Respiratory failure is managed by combined supportive and specific therapies.

B. In hypoxemic respiratory failure, the major problem is a low P_{AO_2}. If the mechanism is low $\dot{V}/\dot{Q}$ mismatch, supplemental O_2 will prove effective. If the disease process involves a diffuse pulmonary intraparenchymal shunt, as in the acute respiratory distress syndrome, mechanical ventilation with positive end-expiratory pressure may be required in addition to supplemental O_2. If the problem is a right-to-left cardiac or pulmonary vascular shunt, supplemental O_2 alone will be of limited benefit; emphasis is on specific therapy (i.e., surgical or minimally invasive repair of an atrial septal defect, obliteration of a pulmonary arteriovenous fistula).

C. The key initial decision in hypercapnic respiratory failure is whether or not the patient requires ventilatory support in the form of noninvasive positive-pressure ventilation or intubation and mechanical ventilation. In general, intubation should be strongly considered for patients with acute

respiratory acidosis that has not rapidly responded to medical therapy or one to two hours of noninvasive ventilation in patients who can maintain their own airway effectively. The patient with a $\Delta H^+/\Delta PaCO_2$ ratio that signifies chronic respiratory acidosis should be followed closely, but these patients uncommonly need to be intubated. In the acute situation, noninvasive mechanical ventilation or intubation will be needed unless specific therapy can immediately reverse the crisis. In the acute-on-chronic situation ($\Delta H^+/\Delta PaCO_2 \sim 0.5$), the trend of the acidosis over time is the crucial factor in deciding on the necessity for intubation.

D. Specific therapy varies greatly by disease, and therefore no broad generalizations can be made. Examples of potential specific therapy include naloxone to reverse respiratory center depression from narcotic overdose, inhaled bronchodilators and systemic corticosteroids for asthma and an acute exacerbation of chronic bronchitis, or nasal continuous positive airway pressure for obstructive sleep apnea. Details of therapy for the most common of these diseases are presented in subsequent chapters.

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The full textbook chapter from which this Manual's summary is based.

40 Acute Respiratory Distress Syndrome

Frantisek Sandor, Mark M. Wilson, and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent a continuum of severity for the same pathologic condition of acute, diffuse alveolar damage (DAD) and pathophysiologically are defined by the presence of increased capillary permeability, pulmonary edema, and refractory hypoxemia due to progressively more severe ventilation–perfusion mismatch and right-to-left shunting.

B. ARDS has an estimated annual incidence in the United States of approximately 79 cases per 100,000 person-years.

C. As of June 2012, the clinical definition ALI and ARDS has changed. This new definition addresses some of the limitations of the previous classification (American-European Consensus Conference, 1994) including clarification of exclusion of hydrostatic edema and provides an increased accuracy of prediction for mortality and duration of mechanical ventilation. There are 4 components of the new Berlin Classification of ARDS.

1. *Timing*: development of ARDS within 1 week of a known clinical insult or appearance of new or worsening of previous respiratory symptoms.
2. *Chest imaging*: bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. These findings may be demonstrated on either computed tomography (CT) scan of the chest or simple chest radiograph (CXR).
3. *Origin of pulmonary edema*: Due to the decline in use of pulmonary artery catheters, the pulmonary artery wedge pressure criterion <18 mm Hg was removed from the definition. If there is no risk factor identifiable for ARDS, an objective evaluation with echocardiogram is required to assist in elimination of a possible hydrostatic edema.
4. *Oxygenation*: ARDS has three categories based on severity of hypoxemia.
   - **a.** Mild ARDS (formerly ALI): 200 mm Hg < Pao_2/Fio_2 < 300 mm Hg.
   - **b.** Moderate ARDS: 100 mm Hg < Pao_2/Fio_2 < 200 mm Hg.
   - **c.** Severe ARDS: <100 mm Hg Pao_2/Fio_2.

II. ETIOLOGY

A. ARDS may be caused by conditions eliciting *lung injury directly* (gastric aspiration, pulmonary contusion, pneumonia, or other toxic inhalational injury) and those that induce *lung injury indirectly* (sepsis, trauma, burns, drug ingestion, pancreatitis, plasma-containing blood products causing transfusion-related acute lung injury [TRALI]). Indirect mechanisms are responsible for most cases of ARDS.

B. Systemic inflammatory response syndrome (SIRS) or sepsis syndrome is responsible for up to 50% of ARDS cases.

C. The risk of ARDS increases as the number of potential causes (risk factors) increases.

III. PATHOPHYSIOLOGY

A. The initial pathology of ARDS is defined by DAD including interstitial and proteinaceous intra-alveolar edema and fibrin deposition. Alveolar flooding typically occurs in only some alveoli; others appear to be normal.

B. Deposition of hyaline membranes within alveoli and degenerative cellular changes occur within 1 to 2 days of the initial insult.

C. Most of the alveolar edema usually resolves after approximately 1 week. Some patients seem to resolve lung injury with little if any fibrosis, whereas others go on to develop severe parenchymal fibrosis. The reason that outcomes are so variable is unknown.

D. The extensive right-to-left shunt in ARDS (up to 25% to 50% of the cardiac output) results from persistent perfusion of atelectatic and fluid-filled alveoli.

E. Respiratory system compliance is significantly reduced due to edema and atelectasis. If fibrosis develops subsequently, the elastic recoil of the lung parenchyma can be permanently increased.

F. The work of breathing in ARDS is increased and may be responsible for up to 25% to 50% of the body's total oxygen consumption. Mechanical ventilatory support in ARDS reduces the work of breathing, so oxygen can be redirected to other vital organs.

G. Due to the variety of conditions associated with ARDS, no characteristic hemodynamic pattern exists. Rather, the hemodynamic pattern reflects the condition that caused the ARDS.

IV. DIAGNOSIS

A. ARDS presenting without preexisting or coexisting conditions is easy to recognize.

B. Most common symptoms include dyspnea and tachypnea that often precede the full development of patchy, heterogeneous bilateral infiltrates on CXR or CT scan of the chest; however, alveolar infiltrates invariably develop within the next several hours.

C. Crackles and scattered rhonchi may be heard throughout the lung fields. Despite severe alveolar infiltrates, often the initial chest examination is remarkably normal.

D. The diagnosis of ARDS is typically made by the above clinical criteria since obtaining lung tissue in critically ill patients is most often not necessary or feasible.

V. TREATMENT

A. Specific treatment.

1. No specific therapy exists for ARDS. Identified underlying or complicating conditions should be treated with specific therapy on an individual basis.

B. Supportive treatment.

1. **Mechanical ventilation.**
   - **a.** In mild ARDS, noninvasive positive pressure ventilation should be considered initially. Should the patient's condition deteriorate further, invasive mechanical ventilation is warranted.
   - **b.** Initial ventilator management generally includes a volume-cycled ventilator in the assist/control mode. Convincing data favor the use of low tidal volumes (Vt) of 6 mL/kg of ideal body weight and keeping airway plateau pressures <30 cm H_2O in an attempt to minimize alveolar overdistension injury. The use of low Vt can lead to atelectasis and hypercapnia (which itself may be therapeutically desirable; see discussions on permissive hypercapnia strategies).
   - **c.** The use of recruitment maneuvers (RM) has yielded mixed clinical results.
   - **d.** When oxygenation goals $Pao_2 \geq 60$ mm Hg cannot be achieved with positive end-expiratory pressure (PEEP) < 15 to 20 cm H_2O or when PEEP induces excessive plateau pressures, prone positioning (see the subsequent text) and/or the pressure-control mode/inverse-ratio mode may be useful strategies to consider to improve gas exchange.
   - **e.** Clinical experience with other nonconventional modes of ventilatory support (high-frequency ventilation, liquid ventilation, extracorporeal membrane oxygenation [ECMO]) is too limited to allow any recommendations on their use. The most recent multi-center clinical trial showed significant (50%) reduction in mortality in ARDS patients with severe hypoxemia who underwent prone positioning early and for long daily sessions.
2. **Patient positioning.**
   - **a.** Because of the heterogeneity of lung infiltrates in ARDS, repositioning the patient into the prone position can improve oxygenation by relieving atelectasis and by improving the distribution of perfusion relative to ventilation. Improvement occurs in approximately 66% to 75% of patients, usually within minutes.
3. **Fluid management.**
   - **a.** While hypernatremia and renal hypoperfusion should be avoided, a restrictive rather than liberal fluid management strategy is recommended.
4. **Corticosteroids.**
   - **a.** Several prospective, multicenter, placebo-controlled studies have shown no benefit to the use of high-dose corticosteroids early in the course of ARDS. Corticosteroids also do not appear to be consistently beneficial if administered during the fibroproliferative phase of ARDS (7 to 10 days after onset). However, available data show that administering corticosteroids 14 days after the onset of ARDS is associated with increased mortality and muscle weakness.
5. **Inhaled nitric oxide (iNO) and inhaled epoprostenol.**
   - **a.** iNO and epoprostenol cause selective pulmonary vasodilation, thus improving ventilation–perfusion matching. Although transiently

improving oxygenation for up to 24 hours, iNO failed to improve outcomes on duration of mechanical ventilation or mortality and is not approved for use in adult ARDS. However, iNO or epoprostenol may have a role as salvage therapy in severe ARDS with refractory hypoxemia.

6. **Other pharmacologic therapies.**
   a. As of yet, no specific medications have been shown to be of benefit in ARDS.

C. Complications.

1. The mortality rate for ARDS has improved over the past 4 decades and is now approximately 30% to 40%, mostly within the first 2 weeks of the illness. More specifically, the predicted mortality based on the Berlin Classification is as follows: mild ARDS, 27%; moderate ARDS, 32%; and severe ARDS, 45%.
2. Many patients with ARDS develop a syndrome of multiorgan dysfunction. Recovery depends on adequate support of vital organ systems. Complications of management are common and include barotrauma, nosocomial pneumonia, deep venous thrombosis, catheter-related infections, and stress-related gastrointestinal bleeding.
3. Outcomes for patients are difficult to predict. The greater the number of failing organ systems, the worse is the prognosis.
4. The median duration of mechanical ventilation in survivors: mild ARDS, 5 days; moderate ARDS, 7 days; and severe ARDS, 9 days.
5. Recent outcomes in research indicates that most ARDS survivors have long-term sequelae, including reduced exercise tolerance and diminished diffusing capacity, as long as 1 year after recovery. Further, many survivors will suffer from depression, anxiety, perceived decline in quality of life, or posttraumatic stress disorder as far as 2 years from recovery.

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41 Asthma Exacerbations

J. Mark Madison and Richard S. Irwin

I. PRINCIPLES

A. Definitions.

1. Asthma is an inflammatory disease of the airways featuring reversible airway obstruction.
2. Asthma exacerbations represent acute or subacute increases in airway obstruction that require a temporary change in treatment to prevent further worsening (moderate exacerbation) or that require urgent action to prevent serious morbidity or mortality (severe exacerbation).
3. Status asthmaticus describes an exacerbation of asthma that fails to improve rapidly (usually within 1 hour) with intensive bronchodilator therapy.

II. ETIOLOGY

A. Triggers of asthma exacerbations: Common triggers include environmental factors such as viral upper respiratory tract infections, inhaled allergens, air pollutants, smoke exposure, and nonsteroidal anti-inflammatory drugs (NSAIDs).

B. Types of asthma exacerbations.

1. Slow-onset attacks (>6 hours of deterioration) are most common (approximately 90%).
2. Sudden-progression attacks (<6 hours of deterioration) are less common (approximately 10%).

III. PATHOPHYSIOLOGY

A. Pathology.

1. Inflammation obstructs the airways by increasing mucus, causing edema and eosinophil infiltration of the airway wall, promoting spasm of smooth muscle, and causing damage to the airway epithelium.
2. Sudden-progression asthma attacks tend to be neutrophil predominate.

B. Physiology.

1. Increased airway resistance leads to hypoxemia.
   a. Ventilation–perfusion inequalities mainly account for hypoxemia.
   b. Atelectasis from mucus plugging can cause right-to-left shunt.
2. Severe, increased airway resistance may lead to hypercapnia because of a patient's inability to sustain the increased work of breathing.

IV. DIAGNOSIS

A. Differential diagnosis.

1. Not all wheezing is due to asthma. Obstruction of the airway at any level by any disease process can produce wheezing and dyspnea.

B. Assessment.

1. Failure to appreciate the severity of obstruction contributes to mortality. The amount of wheezing is a poor way to assess the severity of airway obstruction.
2. History: See Table 41-1 for historical features suggesting the presence of or high risk for severe airway obstruction.
3. Physical examination: See Table 41-1 for findings suggesting severe obstruction.
4. Laboratory.
   a. Pulmonary function tests (PFTs).
      i. Obtain an objective measure of maximal expiratory airflow to assess the severity of obstruction whenever possible (peak expiratory flow rate [PEFR] or forced expiratory volume in 1 second [FEV1]).
      ii. PEFR (or FEV1) <40% of baseline is severe obstruction.

TABLE 41-1 History and Physical Findings Suggesting High Risk for Severe Airway Obstruction

History
Prior ICU admissions for asthma
Prior endotracheal intubation for asthma
Aspirin sensitivity
Frequent or recent emergency department visits
Current or recent systemic corticosteroid use
Seizures or syncope during prior exacerbations
Poor ongoing medical care
Delays in obtaining medical care
Physical examination
Tachycardia (>120 beats per minute)
Tachypnea (>30 breaths per minute)
Diaphoresis
Upright posture in bed
Pulsus paradoxus (>10 mm Hg)
Use of accessory muscles of respiration
Late findings:
Cyanosis
Respiratory muscle alternans
Abdominal paradox
Depressed mental status

b. Assessment of oxygenation.

i. Pulse oximetry if severe distress, PEFR < 40% predicted, or patient unable to perform lung function testing. Oxygen saturation <90% suggests a severe exacerbation.

ii. Consider arterial blood gas (ABG) when alveolar hypoventilation suspected (see Table 41-1), patient is in severe distress, or PEFR (or FEV1) is <25% predicted. A normal P_{CO_2} is a potentially ominous finding that suggests impending respiratory failure.

V. TREATMENT

A. Bronchodilator therapy.

1. β-Adrenergic agonists should be started immediately at presentation.

a. Short-acting, β_2-adrenergic agonists (SABA) (e.g., albuterol) are the mainstay. Four to eight puffs of albuterol by metered-dose inhaler (MDI) with a spacer device can be given every 20 minutes for up to 4 hours and then given every 1 to 4 hours as needed thereafter.

b. Inhaled route of administration is preferable even when severe obstruction is present. When used properly, an MDI with spacer device is as effective as small-volume nebulizer.

2. Cholinergic antagonists.

a. Muscarinic cholinergic antagonists (e.g., ipratropium) should be used as an adjunct to β_2-adrenergic agonists during initial treatment of severe exacerbations in the emergency department. Once the patient is hospitalized, cholinergic antagonists are not recommended.

b. Four to eight puffs of ipratropium by MDI with spacer every 6 hours as needed or 0.5 mg by nebulizer every 6 hours as needed.

3. Methylxanthines.

a. Because of toxicity, methylxanthines are not recommended.

B. Anti-inflammatory therapy with corticosteroids.

1. Corticosteroids are essential for treating acute exacerbations of asthma and should be started at presentation without delay.

2. Oral corticosteroids (e.g., prednisone) are as effective as intravenous therapy (e.g., methylprednisolone). However, for critically ill patients admitted to an intensive care unit, many clinicians prefer the intravenous route because gastrointestinal absorption of drugs may be variable in critically ill patients.

3. For acute exacerbations of asthma, guidelines recommend methylprednisolone, prednisolone, or prednisone at 40 to 80 mg/day in one or two divided doses until PEFR > 70% of baseline.

4. The total course of systemic corticosteroids may be from 3 to 10 days. For courses <7 days, tapering of dose is not necessary. For longer courses, some clinicians prefer gradual tapering. The recovering patient should be started on an inhaled corticosteroid (ICS).

C. Other therapy.

1. Oxygen: Supplemental oxygen therapy should be started immediately. Seemingly paradoxical, inhaled β_2-adrenergic agonists may transiently

worsen ventilation–perfusion matching and cause hypoxemia unless supplemental oxygen is given.

2. Adjunct measures.
   a. Although evidence supporting the practice is mixed, guidelines recommend considering heliox-driven albuterol nebulization to possibly avoid intubation during severe, life-threatening exacerbations. Because heliox affects the inhaled mass of medication and the size of the aerosol particles, the flow to power the nebulizer should be increased when heliox is used.
   b. Guidelines recommend considering intravenous magnesium sulfate to possibly avoid intubation during severe, life-threatening exacerbations but only after conventional measures (see above) have been given.
   c. Administration of adjunct measures should never delay a needed intubation.
3. Mechanical ventilation.
   a. Decision to intubate is based on serial clinical evaluations to assess the response to therapy, whether hypercapnia is worsening, whether there are signs of muscle fatigue, and whether mental status is deteriorating.
   b. Heliox administration may decrease the need for intubation and mechanical ventilation in some acutely ill patients.
   c. Oral, rather than nasal, route of intubation is preferable. Use an endotracheal tube with internal diameter 8 mm or larger, if possible.
   d. Avoid barotrauma due to dynamic hyperinflation during mechanical ventilation. Controlled hypoventilation (or "permissive hypercapnia") is the main strategy that should be used to keep plateau airway pressures <30 cm H_2O. For patients deeply sedated and paralyzed with a neuromuscular blocking agents, monitor lung volumes at end inspiration (VEI) to detect, monitor, and manage dynamic hyperinflation, with the goal of having VEI < 20 mL/kg.
   e. The combination of neuromuscular blocking agents and corticosteroids has been associated with severe myopathy. When paralyzing agents are necessary for ventilating the patient, muscle function always should be allowed to recover partially between repetitive boluses.

D. Additional and unconventional measures: When severe airway obstruction is not responding to conventional therapy and mechanical ventilation, other measures may include helium–oxygen (heliox), general anesthetics (e.g., halothane), bronchoscopy with therapeutic lavage, hypothermia, and extracorporeal life support. Because no mechanical ventilator is calibrated for use with helium, correction factors need to be applied in setting up mechanical ventilation with helium–oxygen mixtures.

E. Therapies with no established role: There is no established role for fluid administration in excess of euvolemia, mucolytics, or chest physical therapy. Sedatives are contraindicated unless the patient is mechanically ventilated. Antibiotics are used only when there is a strong suspicion of active infection.

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The referenced, full textbook chapter from which this Manual's summary is based.

42 Chronic Obstructive Pulmonary Disease

Sean O'Reilly and Deirdre L. Kathman

I. GENERAL PRINCIPLES

A. Chronic obstructive pulmonary disease (COPD): a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

B. COPD frequently results in significant activity limitation, permanent disability, and frequent utilization of costly medical resources.

II. ETIOLOGY

A. Cigarette smoking is the major risk factor. Age at initiation and total number of pack years are associated with the diagnosis.

B. Homozygous α1-antitrypsin deficiency.

C. Other factors that may increase risk include significant childhood respiratory illnesses, outdoor and indoor air pollution (especially cooking with coal, wood, and charcoal), uncontrolled asthma, and occupational dust and chemical exposure.

III. PATHOPHYSIOLOGY

A. Structural (excessive mucus production, mucus gland hypertrophy, and inflammatory edema) and functional airway narrowing (bronchoconstriction, loss of elastic recoil, and destruction of alveoli) causes expiratory airflow limitation.

B. Consequences of severe, chronic airflow obstruction.

1. Reduced flow rates, limiting minute ventilation.
2. Ventilation/perfusion ($\dot{V}/Q$) mismatch.
3. Air trapping, hyperinflation, and increased airway resistance place elevated workloads on the respiratory muscles and can result in muscle fatigue.
4. CO_2 retention due to increased dead space and a shift of the hemoglobin–oxygen binding curve.

IV. DIAGNOSIS

A. History.

1. Cardinal symptoms are chronic productive cough and dyspnea on exertion.

2. The diagnosis is unlikely without history of smoking; however, it develops in a minority of smokers, suggesting some role of host susceptibility.

B. Physical examination.

1. Rarely diagnostic; may include pursed lip breathing, accessory muscle use, decreased breath sounds, prolonged expiration, wheezing, and hyperinflation.

C. Radiology.

1. Chest roentgenogram findings are not sensitive for the diagnosis of COPD.
2. Chest computed tomography (CT) scan is more sensitive for COPD and can demonstrate emphysematous changes, when present, and the nature and extent of disease. It can also be used to screen for patients who might benefit from lung volume reduction techniques.

D. Pulmonary function tests (PFTs).

1. Expiratory airflow obstruction on spirometry that is not fully reversible, as measured by a postbronchodilator ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC).
2. FEV_1/FVC of <0.7 is required to make the diagnosis of COPD.
3. Postbronchodilator FEV_1 correlates with clinical outcome and mortality; not entirely predictive of disease progression and may not correlate with functional status.
4. Hypercapnic respiratory failure in COPD is not usually seen until FEV_1 is <1 L.
5. Increased total lung capacity and residual volume, suggesting air trapping, and/or a reduction in carbon monoxide diffusing capacity may occur.
6. Arterial blood gases (ABGs) diagnose and quantitate the severity of respiratory failure; consider if peripheral oxygen saturation <92% or if concern for hypercapnia.
7. Pulse oximetry should be performed in all stable patients with FEV1 < 35% predicted or with clinical signs of respiratory or right heart failure to assess need for supplemental oxygen.

E. Global Initiative for Chronic Obstructive Lung Disease (GOLD).

1. Consensus workshop report with strategy for diagnosis, management, and prevention of COPD.
2. GOLD guidelines describe a spirometric classification of disease severity. In patients with $FEV_1/FVC < 0.7$, based upon postbronchodilator FEV_1.
   a. Stage I (mild): $FEV_1 \geq 80\%$ predicted.
   b. Stage II (moderate): $50\% \leq FEV_1 < 80\%$ predicted.
   c. Stage III (severe): $30\% \leq FEV_1 < 50\%$ predicted.
   d. Stage IV (very severe): $FEV_1 < 30\%$ predicted.
3. GOLD guidelines also describe a combined assessment of COPD severity that is based on symptoms, spirometric classification, and frequency of exacerbations. The combined assessment is designed to improve management.

F. Acute exacerbation of COPD.

1. Classically marked by one or more of the following:
   a. Increase in severity or frequency of cough.
   b. Increased sputum production or purulence.
   c. Worsening dyspnea.
2. Nearly 70% to 80% of exacerbations are related to upper or lower respiratory infections.
3. Exacerbation frequency varies greatly between patients; tends to increase with worsening airflow limitation.

V. TREATMENT

A. Acute exacerbations.

1. Oxygen therapy is required in all hypoxemic patients (Pao_2 < 60 mm Hg) with an acute exacerbation. Correction of hypoxemia is of prime importance, although the change in $Paco_2$ with Fio_2 should be monitored since hypercarbia may worsen.
2. Bronchodilator therapy.
   a. Short-acting inhaled $beta_2$-agonists with or without short-acting anticholinergic agents are the preferred bronchodilators for the treatment of an exacerbation according to GOLD guidelines. However, the benefit of adding anticholinergic agents to $beta_2$-agonists is not well established by clinical trials.
   b. Delivery by small-volume nebulizer or by metered-dose inhaler (MDI) with a spacer is equally effective.
3. Antibiotics.
   a. Shorten duration of symptoms; decrease short-term mortality and the risk of treatment failure, particularly in more severe exacerbations/hospitalized patients.
   b. Should be directed against organisms typically responsible for acute exacerbations, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis.*
   c. Consider pathogens more difficult to treat, that is, *Pseudomonas* spp., if patient fails to respond to initial antibiotic therapy.
   d. Recommended treatment course 5 to 10 days.
4. Corticosteroids.
   a. Shorten recovery time, improve FEV_1 and arterial hypoxemia, and decrease relapse rate, treatment failure, and length of hospital stay.
   b. For inpatients with severe exacerbations, up to 125 mg of IV methylprednisolone every 6 hours is used as initial therapy. Optimal duration and treatment not established; GOLD guidelines recommend 10 to 14 days of oral prednisolone 30 to 40 mg daily or equivalent.
   c. Studies have indicated that oral steroids might be as effective as those given via the intravenous route for patients without acute respiratory acidosis.
5. Additional therapies.
   a. Nutritional support.

b. Consider and treat conditions that may mimic and/or aggravate exacerbations.

i. Aspiration, gastroesophageal reflux disease, pneumonia, pulmonary embolism (present in 25% of patients admitted for an acute exacerbation of COPD in one meta-analysis), congestive heart failure, cardiac arrhythmia, pneumothorax, and pleural effusions.

B. Respiratory failure.

1. Supplemental oxygen to reverse hypoxemia and tissue hypoxia. Use of low-flow oxygen by nasal cannula or a Venturi mask allows for precise titration of the oxygen concentration necessary to correct hypoxemia and avoid worsening hypercarbia.

2. Indications for ICU admission.

a. Severe dyspnea with inadequate response to initial resuscitative treatment.

b. Altered mental status.

c. Persistent or worsening hypoxemia or respiratory acidosis despite medical therapy.

d. Need for invasive or noninvasive mechanical ventilation.

e. Hemodynamic instability.

3. Noninvasive positive-pressure ventilation (NIPPV).

a. The favored mode of assisted ventilation in patients with respiratory acidosis and/or severe dyspnea with clinical signs of respiratory muscle fatigue.

b. Effectively reduces intubation rate, relieves dyspnea, improves acid–base status, decreases hospital length of stay, and reduces inhospital mortality and longer-term mortality at 1 year.

c. Pressure support ventilation, often begun at an inspiratory positive airway pressure (IPAP) of 8 cm H_2O, an expiratory positive airway pressure (EPAP) of 5 cm H_2O and titrated according to patient comfort up to a goal inspiratory to expiratory pressure difference of 10 cm H_2O to ensure adequate unloading of respiratory muscles. Can begin at maximal pressure (i.e., 15 IPAP, 5 EPAP) if in severe distress and tolerated.

d. Contraindications: respiratory arrest, cardiovascular instability, severely impaired mental status/excessive agitation, recent craniofacial surgery, inability to clear secretions or to protect the airway.

4. Intubation and mechanical ventilation.

a. Indications.

i. Failure of NIPPV: unchanging dyspnea/respiratory distress or worsening ABG within 2 hours.

ii. Severe acidosis (pH < 7.2) and worsening hypercapnia ($Paco_2$ > 60 mm Hg).

iii. Life-threatening hypoxemia (Pao_2/Fio_2 < 200 mm Hg).

iv. Altered mental status or inability to clear secretions and to protect the airway.

v. Hemodynamic instability.

b. Objectives: support of gas exchange and to rest the respiratory muscles.

c. Dynamic hyperinflation or autoPEEP (positive end expiratory pressure) is a dangerous consequence of inadequate ventilator settings and can result in hypotension and cardiovascular collapse. Lower tidal volumes, respiratory rate, and higher inspiratory flow rates will increase time spent in exhalation and decrease autoPEEP but must be titrated carefully to also not worsen respiratory acidosis and hypoxemia. AutoPEEP is measured on the ventilator with an end-expiratory hold maneuver and should be suspected in any patient who develops hypotension on mechanical ventilation for an exacerbation of COPD. In an emergency, disconnecting the patient from the ventilator circuit can be diagnostic and therapeutic.

5. In COPD patients who fail spontaneous breathing trials, see chapter 50 on discontinuation of mechanical ventilation.

VI. PREVENTION OF EXACERBATIONS OF COPD/MANAGEMENT OF STABLE COPD

A. Smoking cessation: the intervention with the greatest capacity to influence the natural history of COPD.

B. Pneumococcal and annual influenza vaccinations have been shown to decrease morbidity and mortality among patients with COPD.

C. Pharmacologic management of COPD is recommended in a stepwise fashion, based upon spirometry, severity of symptoms, and frequency of exacerbations.

1. Reduction in symptoms, frequency, and severity of exacerbations and improved health status and exercise tolerance.

2. Does not modify long-term decline in lung function or decrease mortality.

3. Short-acting bronchodilators (anticholinergic or $beta_2$-agonist) recommended as needed for GOLD stages 1 and 2 without frequent symptoms/exacerbations.

4. A long-acting anticholinergic or a long-acting $beta_2$-agonist is recommended for GOLD stages 1 and 2 with increased symptoms.

5. In GOLD stages 3 and 4, inhaled corticosteroid plus long-acting $beta_2$-agonist and/or long-acting anticholinergic therapy is recommended. These medications have been shown to decrease the frequency of exacerbations.

6. The addition of a phosphodiesterase 4 inhibitor, theophylline, carbocysteine, and/or chronic macrolide therapy may be considered in select patients for improved control.

D. Oxygen therapy used for >15 hours/day in patients with severe COPD and hypoxia is associated with decreased mortality and improved quality of life in patients with either:

1. A Pao_2 < 55 mm Hg or oxygen saturation ≤88%.

2. Pao_2 of 60 mm Hg or oxygen saturation ≤88% with associated polycythemia or right-sided heart failure.

E. Pulmonary rehabilitation programs reduce dyspnea and improve exercise tolerance and quality of life in patients with severe COPD.

F. Assessment and management of comorbidities associated with COPD, such as cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer.

G. Surgical treatments, including lung volume reduction surgery, lung transplantation, or bullectomy may be considered for selected patients.

H. Nocturnal noninvasive ventilation may prolong survival in selected patients with severe COPD and daytime hypercapnia, but with negative impacts on quality of life.

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43 Extrapulmonary Causes of Respiratory Failure

Avani T. Mehta and Mark M. Wilson

I. GENERAL PRINCIPLES

A. The components of the extrapulmonary compartment are the (a) central nervous system (CNS), (b) peripheral nervous system, (c) respiratory muscles, (d) chest wall, (e) pleura, and (f) upper airway.

B. Extrapulmonary compartment impairment causes hypoventilation; the resultant respiratory failure is always hypercapnic.

C. Hypercapnic respiratory failure is due to extrapulmonary causes in up to 17% of cases.

II. ETIOLOGY AND PATHOPHYSIOLOGY

A. Extrapulmonary disorders lead to hypercapnic respiratory failure from a decrease in normal force generation (CNS dysfunction, peripheral nervous system abnormalities, chest wall, pleural disorders, or respiratory muscle dysfunction) or an increase in impedance to bulk flow ventilation (upper airway obstruction).

B. Any condition that impairs respiratory muscle function can result in decreased force generation; if impairment is severe enough, alveolar ventilation may be compromised and $Paco_2$ increased.

C. CNS depressants (narcotics, barbiturates), metabolic abnormalities (hypothyroidism, starvation, metabolic alkalosis), CNS structural lesions, primary alveolar hypoventilation, and central sleep apnea cause either a decrease in central respiratory drive from loss of sensitivity to $Paco_2$ and pH changes or as a result of a peripheral chemoreceptor loss of sensitivity to hypoxia.

D. Disruption of impulse transmission from the respiratory center in the brainstem to the respiratory muscles may result in respiratory failure. The innervation of the inspiratory respiratory muscles may be involved as part of a generalized process, such as in Guillain-Barré syndrome (GBS), myasthenia gravis, amyotrophic lateral sclerosis (ALS), neuromuscular junction blockade, or as an isolated abnormality with variable affects to the respiratory system depending on the level of the injury, such as in phrenic nerve palsy and spinal cord trauma or lesions.

E. Peripheral nervous system dysfunction that causes hypercapnic respiratory failure is always associated with a reduced vital capacity (usually <50% of predicted value) and markedly decreased maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) at the mouth (usually to <30% of predicted). A few examples of this include ALS, poliomyelitis, GBS, paralytic shellfish poisoning, diphtheria, tick paralysis, myasthenia

gravis, Eaton-Lambert syndrome, critical illness polyneuropathy, botulism, and organophosphate poisoning.

F. Certain systemic myopathies feature prominent respiratory muscle involvement, such as muscular dystrophies, myotonic disorders, inflammatory and endocrine myopathies, and electrolyte disturbances (hypophosphatemia, hypermagnesemia/hypomagnesemia, hypokalemia, hypercalcemia).

G. Disorders causing a decrease in chest wall or pleural compliance (kyphoscoliosis, pleural fibrosis, flail chest, obesity–hypoventilation syndrome, ankylosing spondylitis) or increase in airflow resistance from upper airway obstruction (foreign body aspiration, tracheal stenosis, epiglottitis, laryngeal edema, laryngeal/tracheal tumors, obstructive sleep apnea) may culminate in hypercapnic respiratory failure.

H. Scoliosis (lateral spinal curvature) is generally a more important factor in the development of hypercapnic respiratory failure than is kyphosis (dorsal spinal curvature). Severe deformity, defined as angle of lateral curvature 120 degrees or more, poses the greatest risk for development of respiratory failure.

III. DIAGNOSIS

A. Arterial hypercapnia (elevated $Paco_2$) with a normal alveolar–arterial oxygen tension gradient (A–a gradient <20 mm Hg) on room air is, with few exceptions, diagnostic of pure extrapulmonary respiratory failure.

B. The major differential diagnosis of extrapulmonary respiratory failure is hypercapnic respiratory failure from intrinsic lung disease (chronic obstructive pulmonary disease).

C. Pulmonary parenchymal disease can coexist with extrapulmonary respiratory failure, suggested by hypercapnia and widening of the A–a gradient. Primary pulmonary disease causing hypercapnia usually has a gradient >30 mm Hg, but some degree of extrapulmonary dysfunction may exist.

D. A careful medical history should include (but not be limited to) the presence of muscle weakness and specific muscle groups involved, duration of symptoms, sleep pattern and daytime somnolence, history of trauma or recent viral illness, dietary habits, and drug ingestions or chemical exposures.

E. Measurements of MIP and MEP are easy, noninvasive, and highly predictive of the development of hypercapnic respiratory failure in the setting of decreased respiratory muscle force generation. MIP not as negative as –30 cm H_2O or reduced to up to 30% of normal (which varies on basis of age and sex) is likely to be associated with arterial hypercapnia. MEP < 40 cm H_2O is generally associated with a poor cough and difficulty clearing secretions.

F. Vital capacity measurements may be valuable predictors of the development of arterial hypercapnia and can be performed at the bedside. In neuromuscular weakness, vital capacity ≤1 L or <15 mL/kg body weight is commonly associated with arterial hypercapnia; however, this is a less sensitive predictor than the MIP, particularly with chest wall disorders such as kyphoscoliosis.

G. Upper airway obstruction should be considered with complaints of dyspnea with stridor (extrathoracic obstruction) or expiratory wheezing (intrathoracic obstruction), particularly if other symptoms suggest an upper airway

process (e.g., dysphagia in epiglottitis). Upper airway obstruction is usually confirmed in the pulmonary function laboratory by flow-volume loop analysis or by direct visualization.

H. Specific laboratory testing (toxicology screens, thyroid function tests, and levels of magnesium, phosphate, potassium, calcium, and creatinine phosphokinase) and other diagnostic studies (computed tomography, lumbar puncture, electromyography, muscle or nerve biopsy, polysomnogram) should be guided by the patient's presentation and physical examination.

IV. TREATMENT

A. The treatment of extrapulmonary respiratory failure can be divided into specific and supportive therapy. A description of specific therapies for each of the numerous potential causes of extrapulmonary respiratory failure is beyond the scope of this chapter.

B. Supportive therapy involves the use of mechanical ventilatory assistance, supplemental oxygen, and techniques of airway hygiene.

C. In chronic or progressive disease, reversible factors such as pulmonary edema, infection, retained secretions, and other intercurrent illnesses should be carefully sought and treated.

D. Regardless of the primary cause of respiratory muscle weakness, malnutrition exacerbates muscle weakness, and proper nutritional support can be beneficial.

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44 Acute Respiratory Failure in Pregnancy

Mitra Ghasemi and Oren P. Schaefer

I. GENERAL PRINCIPLES

A. Acute respiratory failure is an important cause of maternal and fetal morbidity and mortality.

B. An understanding of normal physiologic changes in pregnancy is important in considering pathophysiology (see Table 44-1).

II. ETIOLOGY

Table 44-2 lists the most important causes of respiratory failure in pregnancy.

A. Thromboembolic disease.

1. Pulmonary thromboembolism: leading cause of maternal mortality in developed world and the second most common cause of mortality (after bleeding) in developing world.

2. Increased risk in pregnancy is an example of Virchow's triad.

- **a.** Hypercoagulability (increases in coagulation factor V, decreased anticoagulant and fibrinolytic activity).
- **b.** Venous stasis (progesterone-induced venodilation, pelvic venous compression by the gravid uterus, and pulsatile compression of the left iliac vein by the right iliac artery).
- **c.** Vascular damage (vascular compression at spontaneous, operative, or assisted delivery).

3. Risks in addition to usual risk factors for venous thromboembolism (VTE) in general population: increased maternal age, multiparity, obesity, assisted reproduction, postpartum hemorrhage, or preeclampsia.

4. Challenges in diagnosis of VTE in pregnancy.

- **a.** Symptoms of VTE mimic the physiologic changes of pregnancy (dyspnea, tachycardia, and leg swelling).
- **b.** D-dimer concentration rises gradually during pregnancy and only returns to normal levels after 4 to 6 weeks postpartum.
- **c.** Potential oncogenic and teratogenic risk incurred due to fetal exposure to diagnostic radiation.
- **d.** Compression ultrasonography in pregnant patients with suspected pulmonary embolism (PE) *without* leg symptoms is associated with an increased likelihood of false-negative results (due to a higher risk of isolated pelvic deep venous thrombosis) and the potential for false-positive findings related to the slow venous flow in pregnancy.

TABLE 44-1 Physiologic Changes in Pregnancy

Pulmonary function	
Expiratory reserve volume	Decreased
Residual volume	Decreased
Functional residual capacity	Decreased
Total lung capacity	Mildly decreased
Inspiratory capacity	Increased
Vital capacity	No change
Tidal volume	Increased
Respiratory rate	No change, mild increase
Minute ventilation	Increased
Peak flow	No change
FEV_1	No change
Lung compliance	No change
Total respiratory compliance	Decreased
Diffusion capacity	Increase followed by decrease
Gas exchange values	
$Paco_2$	Decreased to 28–32 mm Hg
Pao_2	Increased followed by decrease
pH	Increased to 7.40–7.45
Serum bicarbonate	Decreased to 18–21 mEq/L
Alveolar–arterial gradient	Mildly increased
Oxygen consumption	Increased
Carbon dioxide production	Increased

e. Ventilation perfusion scintigraphy: Advantages are the lower amount of radiation exposure to the breasts, the high proportion of normal and near-normal ventilation perfusion scans in pregnant women with suspected PE, and the uncertainty caused by a finding of subsegmental PE on computed tomography (CT) pulmonary angiogram.

f. Chest CT pulmonary angiography: is the preferred first test in hemodynamically unstable pregnant patients, because this test is faster, can rule out other life-threatening diagnoses that mimic PE, and exposes the fetus to less radiation than ventilation–perfusion scintigraph. However, CT pulmonary angiography exposes the mother's breasts to about 150 times more radiation than does ventilation-perfusion scintigraphy.

B. Amniotic fluid embolism.

1. A rare cause of respiratory failure in pregnancy with high morbidity and mortality.
2. Antemortem diagnosis based on clinical setting and exclusion of other causes of respiratory failure.

TABLE 44-2 Causes of Respiratory Failure in Pregnancy

Specific to pregnancy

Tocolytic-induced pulmonary edema
Amniotic fluid embolism
Pulmonary edema due to preeclampsia/eclampsia

Not specific to pregnancy

Pulmonary thromboembolism
Asthma
Gastric aspiration
Pneumonia
Cardiogenic pulmonary edema
Venous air embolism
Acute respiratory distress syndrome (ARDS)
- Due to causes not specific to pregnancy (sepsis, pneumonia, hemorrhage)
- Due to pregnancy-specific complications (preeclampsia/eclampsia, chorioamnionitis, amniotic fluid emboli, placenta abruptio)

Pneumomediastinum and pneumothorax

3. Finding fetal elements in maternal circulation in blood aspirated from right heart catheters lacks both sensitivity and specificity.
4. Dyspnea, tachypnea, tachycardia, and cyanosis during labor or early puerperium are classic. Shock or excessive bleeding may be the first sign. Symptoms may progress to cardiac arrest often within minutes. In those patients who survive the initial event, acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC) are common.

C. Venous air embolism.

1. Rare. Presentation is similar to amniotic fluid embolism.
2. Other potential findings: "mill wheel" murmur and ECG evidence of ischemia, right heart strain, and arrhythmias.
3. Pathophysiology: obstruction of the pulmonary circulation by air that blocks the apical tract of the right ventricle and by fibrin microemboli that obstruct pulmonary arterioles and capillaries.

D. Gastric aspiration.

1. Clinical syndromes include hypoxia/respiratory failure, chemical pneumonitis, pneumonia from aspiration of oropharyngeal bacteria, acute bronchospasm, and ARDS.
2. Potential clinical courses.
   a. Rapid improvement over 4 to 5 days.
   b. Initial improvement followed by deterioration caused by supervening bacterial pneumonia.
   c. Early death due to intractable hypoxemia.

3. Risk factors: increased intra-abdominal pressure caused by gravid uterus, progesterone-induced relaxation of the lower esophageal sphincter, delayed gastric emptying during labor, and analgesia-induced decreased mental status.

E. Respiratory infections.

1. Community-acquired pneumonia: Causal organisms are similar to those of the nonpregnant population.
2. Influenza, varicella, coccidioidomycosis, tuberculosis, listeriosis, and severe acute respiratory syndrome (SARS) have been associated with increased maternal and fetal morbidity and mortality.
3. Primary varicella–zoster infection may progress to pneumonia more commonly than seen in the nonpregnant patient.
4. Listeriosis is rare; commonly results in abortion or neonatal sepsis.

F. Asthma.

1. The most common respiratory problem during pregnancy.
2. Treatment of asthma exacerbation in pregnancy and predictors of hospitalization similar to those of the nonpregnant patient.

G. Tocolytic-induced pulmonary edema.

1. β-Adrenergic agonists are used to inhibit preterm labor.
2. β_2-Selective agents (ritodrine, terbutaline) have diminished the frequency of maternal tachycardia, but pulmonary edema remains a serious side effect.
3. Newer tocolytics including cyclooxygenase-2 inhibitors and oxytocin antagonists are more specific for preterm labor and less likely to cause pulmonary edema than β-agonists.
4. Presentation: chest discomfort, dyspnea, tachypnea, rales, and edema on chest radiograph (CXR).
5. May develop after 24 hours, but usually after 48 hours of therapy.

H. Pneumomediastinum and pneumothorax.

1. Most often seen in the second stage of labor.
2. Presentation: chest or shoulder pain that radiates to neck and arms, mild dyspnea, and subcutaneous emphysema.
3. Prolonged, dysfunctional labor is a predisposing factor.

III. DIAGNOSIS

A. Radiology.

1. No appreciable increased risk of gross congenital abnormalities or intrauterine growth retardation with exposure to <5 to 10 rads. Oncogenic risk is also small; risk of leukemia may be increased (1 per 2,000 vs. background rate 1 per 3,000).
2. Shielding of the abdomen reduces risk further.
3. Estimated fetal radiation exposure: CXR < 1 mrad, chest CT 0.3 to 13 mrad (varies per trimester), pulmonary angiography < 50 mrad, and perfusion lung scan 6 to 12 mrad. The average fetal radiation dose with CT is less than that with $\dot{V}/\dot{Q}$ lung scanning during all trimesters.

IV. TREATMENT

A. Supportive therapy.

1. Intubation and mechanical ventilation (MV): Guidelines for intubation and MV are the same as for nonpregnant patient. There are normal changes in pregnancy that need to be considered for intubation and MV in pregnancy (Table 44-3).
   a. MV of pregnant patients with ARDS should follow the guidelines of the ARDS Network study (see Chapters 43 and 53).
   b. Weaning in the lateral decubitus position may be preferable to avoid compression of the inferior vena cava (IVC) by the gravid uterus.
2. Reversal of hypotension.
   a. Trendelenburg position may further decrease venous return due to IVC compression by the uterus.
   b. Position with right hip elevated 10 to 15 cm (15 degrees) or in the lateral decubitus position.
   c. Hypotension unresponsive to repositioning and fluid resuscitation requires vasopressors. Ephedrine had previously been considered the vasopressor of choice in obstetric patients. Phenylephrine is increasingly being used as recent studies suggest that it improved fetal acid–base status with its use.
3. Nutrition.
   a. Maternal malnutrition correlates with intrauterine growth retardation and development of preeclampsia.
   b. If delivery occurs while mother is receiving total parenteral nutrition, observe the neonate closely for hypoglycemia.

TABLE 44-3 Specific Issues in Intubation and Mechanical Ventilation in Pregnancy

Intubation

- Upper airway hyperemia can make intubation difficult. May need smaller endotracheal tube and more experienced practitioner.
- Decreased functional residual capacity (FRC) and associated microatelectasis may cause sudden hypoxia with short period of apnea: Preoxygenate with 100% oxygen before intubation.
- Increased risk of aspiration: Apply cricoid pressure to decrease gastric inflation.

Mechanical ventilation

- Hypoxia poorly tolerated by fetus: Aim for Pao_2 of more than 95 mm Hg.
- Removal of CO_2 from fetal circulation depends on keeping maternal $Paco_2$ 28–32 mm Hg (permissive hypercapnia should be avoided if possible).
- Persistent hypocapnia with respiratory alkalosis (pH > 7.48) may result in uterine artery vasoconstriction and decreased fetal perfusion.

B. Specific therapy.

1. Thromboembolism.
   - **a.** Low molecular weight heparin (LMWH) is the drug of choice because of practical advantages over unfractionated heparin (UFH) and because of a lower risk of side effects including probably lower risk of osteopenia, bleeding, and thrombocytopenia.
   - **b.** Pregnancy and the immediate postpartum period are relative contraindications to thrombolysis but can be considered with life-threatening embolism.
   - **c.** IVC filter: Indications in general are the same as in nonpregnant patients. One difference is a fresh deep venous thrombosis (i.e., after 37 weeks gestation), especially in the pelvic or proximal veins, that has increased likelihood of embolization during labor. Temporary retrievable inferior vena caval filters are used most appropriately in this setting.
   - **d.** Longer-term anticoagulation.
     - **i.** Because of different pharmacokinetic properties during pregnancy, the effect of LMWH should be closely monitored, aiming for target anti–factor Xa concentrations of 0.5 to 1.1 units/mL 3 to 6 h postdose. Weekly anti–factor Xa concentrations can be measured until they reach therapeutic levels, with subsequent monthly monitoring after the 1st month.
     - **ii.** If used instead of LMWH, UFH should be given for at least 5 days, then administer subcutaneously in doses adjusted to prolong the activated partial thromboplastin time (aPTT) to 1.5 to 2.5 times control.
     - **iii.** Warfarin is a potent teratogen and should not be used.
     - **iv.** Continue therapy throughout pregnancy and at least 4 to 6 weeks postpartum.
     - **v.** For pulmonary thromboembolism in the late pregnancy or postpartum period, continue anticoagulation at least 3 months.
     - **vi.** There are limited data on efficacy of fondaparinux in pregnancy, but bleeding risk is not absent, and care is required when used as second-line therapy.
2. Amniotic fluid embolism: See Table 44-4.
3. Respiratory infections.
   - **a.** Antibiotics are similar to those used for nonpregnant patients.
   - **b.** For community-acquired pneumonia: Penicillins, cephalosporins, azithromycin, and erythromycin (excluding the estolate) are safe.
   - **c.** Other infections are treated according to usual standards; the safety of drug therapy weighed against the risk of untreated infection.
4. Asthma.
   - **a.** Pharmacotherapy is similar to that used for the nonpregnant patient.
   - **b.** High doses of β-agonist carry risk of hypokalemia and pulmonary edema.
   - **c.** With life-threatening refractory asthma, consider emergency delivery of the fetus by C-section. Decision in part depends on age and viability of the fetus.

TABLE 44-4 Specific Treatments for Different Causes of Respiratory Failure in Pregnancy

Pulmonary thromboembolism	• LMWH or IV heparin • Pregnancy and immediate postpartum period are relative contraindications for thrombolysis. • IVC filter in special cases (see text)
Amniotic fluid embolism	• Supportive care—ventilation, oxygenation, BP support, management of bleeding • Extracorporeal membrane oxygenation can be lifesaving for cardiorespiratory collapse.
Venous air embolism	• Left lateral decubitus position • Providing 100% oxygen to help decrease size of emboli • Aspiration of air with central venous or PA catheter can be attempted but rarely needed.
Gastric acid aspiration	• Supportive care—prophylactic antibiotics or corticosteroids not beneficial • Treat with antibiotics only if infection complicates chemical pneumonitis.
Asthma	• Consider intubation with $Paco_2$ of ≤35 mm Hg because baseline $Paco_2$ is depressed in pregnancy and this may mean fatigue and impending respiratory failure. • IV corticosteroids and bronchodilators
Tocolytic-induced pulmonary edema	• Discontinuation of tocolytic agent • Supplemental O_2 • Diuresis
Pneumothorax	Chest tube insertion if • Patient is symptomatic • Presence of mechanical ventilation • Enlarging pneumothorax • Pneumothorax >20% of hemithorax
Pneumonia	• Antibiotics

5. Pneumomediastinum and pneumothorax.
   a. Pneumomediastinum.
      i. Spontaneous resolution is usual in 3 to 14 days; almost never requires drainage. Treatment is directed at the underlying cause (e.g., asthma or increased intrathoracic pressure).
   b. Pneumothorax: See Table 44-4.

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45 Managing Hemoptysis

Paulo J. Oliveira and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Definitions.

1. Hemoptysis: expectoration of blood from the lungs or airways below the glottis.
2. Massive hemoptysis.
   a. Volumetric: most often quoted as expectoration of 600 mL of blood within 24 to 48 hours.
   b. Magnitude of effect: clinical (hemodynamic and respiratory compromise) consequences of hemoptysis.
      i. Mortality related to asphyxiation not exsanguination typically.
3. Pseudohemoptysis: expectoration of blood from other than the lower respiratory tract (e.g., ENT source with epistaxis or upper GI bleed).

II. ETIOLOGY

A. Nonmassive hemoptysis: Table 45-1 lists the common causes of hemoptysis, including bronchitis, bronchiectasis, lung carcinoma, and tuberculosis.

B. Massive hemoptysis.

1. All causes of hemoptysis may result in massive hemoptysis. The most frequent causes are infection (tuberculosis, mycetoma, bronchiectasis, lung abscess), lung cancer, and diffuse intrapulmonary hemorrhage.
2. Catastrophic, albeit rare, causes include rupture of a pulmonary artery from a balloon flotation catheter and tracheoarterial fistula (consider, until proven otherwise, in massive hemorrhage typically occurring 3 days to 6 weeks after tracheostomy).

C. Idiopathic or cryptogenic hemoptysis.

1. Despite a systematic diagnostic approach, hemoptysis may be idiopathic in 2% to 32%.
2. Most commonly seen in men between ages of 30 and 50 years and smokers.
3. Usually presents as nonmassive hemoptysis but can be massive.
4. Ten percent have recurrence and may require vigilant monitoring for potential and eventual diagnosis of underlying malignancy.
5. Consider Dieulafoy disease of bronchus (superficial, ectatic bronchial artery) in the context of cryptogenic hemoptysis presenting with massive hemoptysis.

TABLE 45-1 Common Causes of Hemoptysis[a]

- Tracheobronchial disorders
  - Acute tracheobronchitis
  - Bronchiectasis
  - Bronchogenic carcinoma
  - Chronic bronchitis
  - Gastric acid aspiration
  - Cystic fibrosis
  - Tracheobronchial trauma
  - Tracheoarterial fistula
- Cardiovascular disorders
  - Congestive heart failure
  - Mitral stenosis
  - Pulmonary arteriovenous fistula
  - Pulmonary thromboembolism
- Hematologic disorders
  - Anticoagulant therapy
  - Thrombocytopenia
  - Disseminated intravascular coagulation
- Localized parenchymal disease
  - Acute and chronic pneumonia
  - Aspergilloma
  - Lung abscess
  - Pulmonary tuberculosis
- Diffuse alveolar hemorrhage
  - Goodpasture's syndrome
  - Systemic lupus erythematosus
  - Trimellitic anhydride toxicity
  - Cocaine inhalation
  - Viral pneumonitis
  - Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
  - Bone marrow transplantation
  - Pulmonary capillaritis
- Other
  - Idiopathic
  - Iatrogenic (e.g., bronchoscopy, cardiac catheterization)

[a]This list is not meant to be all inclusive. See Hemoptysis chapter in *Intensive Care Medicine*, 7th edition in Selected Readings for an expanded list with references.

III. PATHOGENESIS

A. Bronchial arterial circuit supplies blood to the airways (main stem bronchi to the terminal bronchioles), pleura, intrapulmonary lymphoid tissue, and large branches of the pulmonary vessels and nerves in the hilar regions. The bronchial circulation is responsible for bleeding in approximately 90% of cases.

B. Pulmonary arterial circuit supplies the pulmonary parenchymal tissue, including respiratory bronchioles.

C. Nonbronchial systemic arteries can also be involved when collateral circulation develops in regions of chronic inflammation.

IV. DIAGNOSIS

A. Medical history.

1. Consider frequency, timing, duration, anticoagulant use, illicit drug use, exposure history, immune system status, and epidemiologic factors including travel history (tuberculosis, endemic fungi, parasites).
2. Chronic sputum suggests chronic bronchitis, bronchiectasis, or cystic fibrosis.
3. Orthopnea and paroxysmal nocturnal dyspnea suggest cardiac failure or mitral stenosis.
4. Always consider pulmonary thromboembolism (generally not a contraindication to anticoagulation).
5. Consider suction catheter trauma.
6. Diffuse alveolar hemorrhage (DAH): hemoptysis typical but absence does not rule this out. Hemoptysis present in only approximately 40% of DAH patients.

B. Physical examination.

1. Evaluation of the respiratory system.
   a. Inspection: evidence of recent or old chest trauma.
   b. Auscultation.
      i. Unilateral wheeze or crackles suggest localized disease.
      ii. Diffuse crackles in congestive heart failure (CHF) and diffuse alveolar hemorrhage.
2. Evaluation of other systems.
   a. Skin and mucous membranes.
      i. Telangiectasias suggest hereditary hemorrhagic telangiectasia.
      ii. Ecchymoses and petechiae suggest hematologic abnormality.
   b. Neck: With pulsations transmitted to a tracheostomy cannula, consider a tracheoarterial fistula or the risk of one.
   c. Cardiovascular: mitral stenosis, pulmonary artery stenosis, or pulmonary hypertension.

C. Laboratory studies.

1. Chest radiograph (CXR).
   a. Obtain in every patient (may suggest diagnosis or help localize bleeding site).
      i. Do not assume that an abnormality always accurately identifies the site of bleeding because spillover/soilage into areas of "normal" lung may occur and/or the seemingly obvious lesion may not be the one that is bleeding.
   b. CXR normal in up to 30%. Only identifies source in 40% to 50% of cases.

2. Complete blood count may suggest infection, hematologic disorder, or chronic blood loss.
3. Urinalysis may show hematuria and active urinary sediment may suggest systemic disease associated with diffuse alveolar hemorrhage (vasculitis, pulmonary–renal syndrome, antiglomerular basement membrane antibody–mediated disease).
4. Coagulation studies: primary or contributing hematologic disorder.
5. Electrocardiogram; consider echocardiogram (CHF, mitral stenosis).
6. Chest computed tomography.
   a. High-resolution chest computed tomography (HRCT) scan may improve yield of bronchoscopy in localizing a bleeding source and point to a diagnosis (especially useful with bronchiectasis).
   b. The use of multidetector computed tomography angiography (MDCTA) not only can help with localization and diagnosis but also is very useful in identifying the culprit vessels (both bronchial and nonbronchial sources) involved and providing a "road map" for the interventional radiologists prior to formal angiographic interventions.
7. Additional evaluation based on history and examination may be warranted (e.g., serologic studies for connective tissue disease/vasculitis, renal function studies, liver function tests, illicit drug screens).

D. Bronchoscopy.

1. For diagnosis and localization of the hemoptysis.
   a. Provides complementary information to CT.
   b. Specifically useful with identifying small endobronchial lesions.
2. Greatest yield when performed during or within 24 hours of active bleeding.
   a. With active bleeding, localization in up to 91%.
   b. Within 48 hours, localization drops to 51%.
   c. After bleeding stops, localization reduced further.
3. Flexible bronchoscopy: ideally used to diagnose lower respiratory tract problems and helpful when considering possible infectious etiology (assist with obtaining appropriate specimens).
4. Rigid bronchoscopy: ideally used for massive hemorrhage (more secure airway with better suctioning capabilities).

V. TREATMENT

A. General considerations.

1. Quantify the amount and rate of bleeding; massive hemoptysis is associated with significant mortality.
2. Consider the cause of bleeding.
3. Consider the patient's underlying lung function (pulmonary reserve) and other comorbidities such as cardiac disease.

B. Supportive care.

1. Bed rest and mild sedation.
2. Cough suppressants should not be used.

3. Supplemental oxygen may be required.
4. Evaluate need for endotracheal intubation early and often (airway protection, assisted mechanical ventilation).
5. If intubation is required, an endotracheal tube with an internal diameter of at least 8.0 mm or even larger will facilitate flexible bronchoscopy and pulmonary toilet.
6. Assure adequate intravenous access. Fluid and blood resuscitation as indicated.
7. Correct any underlying coagulopathies.
8. Chest physical therapy and postural drainage should be avoided.

C. Definitive care.

1. For nonmassive hemoptysis, treatment is directed at the specific cause.
2. Massive hemoptysis is an emergency. The likelihood of death, primarily due to asphyxiation, is directly related to the amount and rate of bleeding.
   a. Treatment aimed at the specific cause.
   b. Treatment aimed to stop the bleeding.
   c. Lung isolation.
      i. Initial management requires protection of the uninvolved lung from aspiration of blood.
      ii. The bleeding lung should be kept dependent (lateral decubitus position with bleeding side down).
      iii. Placement of a double-lumen endotracheal tube (ETT) can favorably affect bronchial isolation, but these tubes can be difficult to place and may be dislodged easily and their small diameter may prevent subsequent bronchoscopy. Selective mainstem intubation into the nonbleeding lung with a single-lumen ETT can also be considered. Guidance with flexible bronchoscopy is recommended.
      iv. Bronchial blockers can be placed endoscopically.
   d. Rigid bronchoscopy under general anesthesia may be required to clear the airway of aspirated blood and provide a secure airway. Once the rigid bronchoscope is inserted, it is typically used in conjunction with a therapeutic flexible bronchoscope.
   e. Therapeutic maneuvers: bronchoscopy (temporizing).
      i. Fogarty balloon catheter or dedicated endobronchial blocker (e.g., Arndt blocker), bronchoscopically positioned, may provide effective tamponade when the bleeding bronchial segment is located.
      ii. Iced saline lavage of the bronchus leading to the bleeding site may stop hemorrhage by local vasoconstrictor effect.
      iii. Other endobronchial hemostatic agents have been used with varied, anecdotal success such as topical vasoconstrictive agents (epinephrine), fibrinogen–thrombin mixtures, cyanoacrylate glue, and more recently, with good success, the application of oxidized regenerated cellulose inserted into lobar and segmental regions of bleeding.
      iv. Laser coagulation and electrocautery can be used to control bleeding in patients with visible bleeding endobronchial lesions. Recurrence of bleeding within a few weeks is typical. Cryotherapy can assist in removing large clots and casts.

f. Therapeutic maneuvers: angiography.
  i. Over the last two to three decades, this has become the first-line modality in the multidisciplinary management of massive hemoptysis. Local expertise and availability is essential for successful implementation. It serves as a definitive intervention and as a bridge while stabilizing the patient and contemplating candidacy for possible surgical intervention.
  ii. Embolization (BAE—bronchial arterial embolization) can successfully stop bleeding in massive hemoptysis in >90% of cases. Rebleeding within 1 to 4 days can occur, and therefore multiple procedures may be necessary. Within 6 months, 20% of patients bleed again. Rebleeding and recurrence should also prompt search for other feeder vessels such as nonbronchial systemic arterial collaterals and the pulmonary arteries as a contributing source. Failure and recurrence rates depend on the underlying etiology (mycetomas and, occasionally, bronchogenic cancer respond poorly).
  iii. Complications that are rare, but serious, include embolization of the spinal arteries and transverse myelitis (in 5% of population, spinal artery originates as a branch of the bronchial artery). Most common adverse reaction is transient chest pain.

g. Specific maneuvers for uncommon causes of massive hemoptysis.
  i. Rupture of the pulmonary artery from pulmonary artery catheter: Deflate balloon, withdraw catheter 5 cm, reinflate balloon with 2 mL of air, allow balloon to float back, and occlude vessel. The catheter usually floats to the right pulmonary artery. If not known which artery has ruptured, place patient in the right lateral decubitus position. Once the patient has been stabilized, study the patient angiographically. If a pseudoaneurysm has formed, ablate the feeding vessel with a coil.
  ii. Tracheoarterial fistula: Overinflation of the tracheostomy cuff or digital insertion into the stoma with manual finger tamponade/compression of the innominate artery against the sternum once intubated beyond the source of bleeding may stop the hemorrhage while mobilizing cardiothoracic and vascular surgery to the operating room.

h. Emergency and elective surgery.
  i. With the exception of immediate intervention to repair a tracheoarterial fistula or pulmonary artery rupture, the role of emergency surgery remains controversial due to the high mortality associated with emergency surgery and inability to accurately assess the patient's cardiopulmonary reserve. Consider in patients who have failed to respond to multiple, repeated embolizations with localized disease who are operable candidates.
  ii. Elective surgery is considered the approach of choice in patients with adequate functional status once bleeding has been stabilized and temporized (BAE, bronchoscopic interventions, etc.) in the following conditions: arteriovenous malformations, chest trauma, mycetoma, localized bronchiectasis, hydatid cyst, or thoracic aneurysm.

i. Conservative nonsurgical treatment.
   i. Advocated when hemoptysis has an infectious cause.
   ii. In patients with cystic fibrosis, as recurrent hemoptysis in other areas is likely, and pulmonary reserve is typically compromised.
   iii. Severe lung disease: When forced expiratory volume in 1 second (FEV1) is <2 L, withhold surgery if assessment suggests a postoperative severe respiratory impairment (FEV1 ≤ 800 mL).
   iv. Palliative radiation therapy can be considered for hemoptysis due to intractable/inoperable lung cancer.
   v. Immunologically mediated disease causing diffuse alveolar hemorrhage.

D. Individualized approach to management.

Therapy in a given patient depends on etiology, lung function, availability of resources, and local expertise. Basic tenets of managing massive hemoptysis include (i) stabilization (airway, hemodynamics, resuscitate),(ii) localization/lateralization (CXR, CT scan, bronchoscopy), and (iii) containment (endobronchial blockers, BAE/angiography) with potential for definitive treatment and surgery in specific cases.

1. Nonsurgical candidates: poor lung function, significant comorbid illness, diffuse lesions. Treat with selective angiography and embolization.
2. Surgical candidates: Resectional surgery should be performed when it will be the definitive treatment for the underlying disease.
3. Diffuse alveolar hemorrhage.
   a. Selective arterial embolization and surgery are not options.
   b. For immune-mediated diseases (e.g., Goodpasture syndrome, systemic lupus erythematosus [SLE], ANCA-associated vasculitides), high-dose steroids and cytotoxic agents are recommended. May also need to consider plasma exchange/plasmapheresis and/or intravenous immunoglobulin (IVIG) in refractory vasculitis-associated hemorrhage.
   c. Post–bone marrow transplantation alveolar hemorrhage requires high-dose steroids.
   d. Consider recombinant activated factor VII or tranexamic acid as a temporizing measure in unstable patients without coagulopathic bleeding.

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46 Aspiration and Drowning

Nicholas A. Smyrnios and Richard S. Irwin

I. ASPIRATION

A. General principles.

1. Definition.
Aspiration: inhaling fluid or a foreign body into the bronchi and lungs. The material may be particulate matter (food particles), fluids, or oropharyngeal secretions containing infectious agents.

2. Aspiration syndromes.
Syndromes caused by aspiration are determined by (a) the material aspirated, (b) the amount aspirated, and (c) the state of the patient's defenses at the time of the event. The various syndromes caused by aspiration are listed in Table 46-1.

B. Pathogenesis.

1. Normal gastrointestinal and respiratory defenses against aspiration. An aspiration event requires bypassing or overwhelming one or more of these mechanisms.

- **a.** Swallowing mechanism: Hypopharyngeal muscles move food into the esophagus, the epiglottis covers the larynx, the vocal cords close, and the upper esophageal sphincter relaxes. Pharyngeal swallowing initiates peristaltic waves in the esophagus that carry the bolus through a relaxed lower esophageal sphincter (LES) to the stomach. The LES then closes to minimize gastroesophageal reflux.
- **b.** Aerodynamic filtration—nose, mouth, and larynx—filter particles greater than 10 μm in diameter.
- **c.** Mucociliary clearance: removes particles 2 to 10 μm in diameter.
- **d.** Alveolar detoxification: alveolar macrophage and neutrophil nonspecific killing for particles <2 μm in diameter.
- **e.** Cough: provides clearance when mucociliary clearance is inadequate.
- **f.** Immunologic mechanisms: These augment the nonimmunologic mechanisms listed above.

2. Factors predisposing to aspiration in critically ill patients.

- **a.** Translaryngeal intubation: Swallowing impairment persists after extubation but usually improves within days to a week.
- **b.** Tracheostomy: interferes with proper laryngeal elevation necessary for glottic closure. Inflated balloon can obstruct esophagus.

TABLE 46-1 Aspiration Syndromes

Mendelson syndrome
Foreign body aspiration
Bacterial pneumonia and lung abscess
Chemical pneumonitis
Exogenous lipoid pneumonia
Recurrent pneumonias
Chronic interstitial fibrosis
Bronchiectasis
Mycobacterium fortuitum or *chelonei* pneumonia
Diffuse aspiration bronchiolitis
Tracheobronchitis
Tracheoesophageal fistula
Chronic persistent cough
Bronchorrhea
Drowning

c. Enteral feeding tubes: can cause vagally induced LES relaxation and also prevent mechanical closure of the LES.
d. Large residual volumes in stomach: Exact volume is unknown, presumed to be approximately 200 mL.

C. Diagnosis.

1. Diagnostic tests available for aspiration are listed in Table 46-2.

TABLE 46-2 Diagnostic Evaluation for Aspiration Syndromes

History
Physical examination
Baseline examination
  Observation of patient drinking water
Complex swallowing evaluation performed by speech pathologist
Chest radiographs
Lower respiratory studies
  Expectorated samples
  Protected specimen brush with quantitative cultures
  Bronchoalveolar lavage
  Lung biopsy
Upper gastrointestinal studies
  Contrast films/modified barium swallow
  Endoscopy
  Scintiscan
  24-h esophageal pH/impedance monitoring
Speech and swallowing bedside methods for detecting aspiration in tube-fed patients

D. Treatment.

1. Mendelson syndrome: Aspiration of gastric contents may cause the development of acute respiratory distress syndrome (ARDS). Management of ARDS is described in Chapter 40.
2. Foreign body aspiration.
   a. Particles that do not totally obstruct the trachea can be removed by bronchoscopy.
   b. Completely obstructing particles can be removed by subdiaphragmatic thrusts in unconscious patients or chest thrusts in obese or pregnant patients.
3. Bacterial pneumonia and lung abscess.
   a. Community-acquired pneumonias are most often due to *Streptococcus pneumoniae*. Lung abscesses are most often due to anaerobes. Both require appropriate antibiotic therapy. Lung abscess patients may require correction of periodontal disease and alcohol abuse treatment.
   b. Nosocomial pneumonias are most often (≥75%) due to enteric gram-negative bacilli and *Staphylococcus aureus*.
   c. Speech pathologist can assess risk of aspiration and help a patient to develop strategies for swallowing that minimize the risk of further aspiration. When either an endotracheal or tracheostomy tube has been in place, oral nutrition should not be started until the patient has a successful speech and swallowing evaluation.
4. Chemical pneumonitis: rapid, self-limited course requires no specific treatment.
5. Exogenous lipoid pneumonia.
   a. Caused by aspiration of oil or fat from animal, plant, or mineral.
   b. Usually resolves without specific treatment.
   c. Preventive measures.
      i. Patients with swallowing problems may require stoppage of oral feedings and initiation of gastrostomy or jejunostomy feedings.
      ii. Elevate head of bed to 45-degree angle during tube feedings.
      iii. Gastroesophageal reflux disease treatment: head-of-bed elevation; acid suppression; prokinetic drugs; antireflux diet; nothing to eat for 3 hours before bedtime.
6. Tracheobronchitis.
   a. Intensive care unit patients generally stop aspirating when oral intake is stopped. Do not resume until modified barium swallow with speech and swallowing evaluation confirms swallowing without aspiration.

II. DROWNING

A. General principles.

1. Definitions.
   a. Fatal drowning: death from suffocation by submersion in water.
   b. Nonfatal drowning: survival, at least temporarily, after respiratory impairment by submersion in water.
   c. Submersion or immersion injury includes both fatal drowning and nonfatal drowning.

2. Statistics.
   a. Seventh most common cause of accidental injury death in the United States.
   b. More than 3,500 fatal drownings in the United States annually.
   c. Incidence 1.21 per 100,000.
   d. Most common in children younger than 14 years, males, Native Americans, African Americans.

B. Risk factors.

1. Alcohol: is the number one risk factor; 30% to 70% of cases are associated with alcohol.
2. Inadequate adult supervision: Pool, bathtub, and large industrial buckets are common sites of childhood immersions. Fences, sign posting, educational programs, and lifeguards minimize risk and improve survival.
3. Child abuse: 29% to 38% of pediatric submersions are related to abuse or neglect.
4. Seizures: Submersion occurs more frequently in children with epilepsy, perhaps due to poor adherence to anticonvulsant regimen.
5. Boating: Restrictions on alcohol and the use of personal flotation devices are associated with fewer events.
6. Aquatic sports: Diving, surfing, and waterskiing implicated. Diving and sliding headfirst produce most serious injuries. Injury related to personal watercraft is becoming more common.
7. Recreational drug use: induces sleep and disorientation, impairs coordination and swimming.

C. Pathogenesis.

1. Anoxia.
   a. Drowning sequence: panic, breath holding, struggle to surface, and a period of intense laryngospasm. The laryngospasm eventually abates, followed by involuntary breaths and aspiration of water in nearly all cases.
2. Hypothermia.
   a. Produces both favorable and unfavorable effects.
   b. For survival after long-term submersion, the core body temperature must be reduced quickly and brain metabolic activity slowed rapidly to prevent damage.
   c. Hypothermia can cause death in three ways.
      i. Vagally mediated asystolic cardiac arrest (immersion syndrome).
      ii. Hypothermia-induced arrhythmia (separate from immersion syndrome) and cardiac arrest from ventricular fibrillation below 25°C and asystole below 18°C.
      iii. Loss of consciousness and aspiration as head falls into water leading to anoxia.
3. Pulmonary effects.
   a. Atelectasis due to increased surface tension.
   b. Bronchoconstriction.
   c. Noncardiogenic pulmonary edema/ARDS.
   d. Fresh water inactivates existing surfactant and prevents production for 24 hours.

e. Hypertonic seawater draws fluid from plasma into the alveoli, causing pulmonary edema. May also damage type II pneumocytes.
f. Aspiration of gastric contents and particles in fresh water and saltwater may lead to ARDS.
g. Postcardiopulmonary resuscitation (CPR) damage, barotrauma, pneumonitis, central apnea, and O_2 toxicity.

4. Neurologic effects.
   a. Greatest effect on prognosis. central nervous system (CNS) injury due to anoxia.
   b. The time course of anoxia is uncertain. Duration of submersion is often unclear, and hypothermia may have a protective effect.
   c. Histology: Edema, necrosis, and mitochondrial swelling are present in the cortex, hippocampus, and cerebellum.
   d. Severe anoxic encephalopathy with persistent coma, seizures, delayed language development, spastic quadriplegia, aphasia, and cortical blindness has been reported.
   e. Virtually all patients who present with fixed, dilated pupils and coma fail to survive.
5. Musculoskeletal effects.
   a. Children with anoxic encephalopathy often develop musculoskeletal problems such as contractures, hip subluxation/dislocation, and scoliosis.
6. Serum electrolytes: minimal impact of electrolyte changes whether fresh water or saltwater drowning because humans rarely take in enough fluid to cause problems and easily correct small changes that do occur.
7. Hematologic effects: Patients rarely require medical intervention for anemia.
8. Renal effects.
   a. Acute tubular necrosis, hemoglobinuria, and albuminuria have been reported.
   b. Diuresis not necessarily due to hypothermia because it is seen in submersion at any temperature.
   c. Metabolic acidosis is frequently present as a result of lactate accumulation.
9. Cardiac effects.
   a. Atrial fibrillation and sinus dysrhythmias are common but rarely require therapy.
   b. PR, QRS, QT prolongation, and J-point elevation are associated with hypothermia.
   c. Death is due to ventricular fibrillation or asystole.
   d. Submersion causes transient increases in central venous and wedge pressures with decreased cardiac output.
10. Infectious complications.
    a. Pneumonia is the predominant infection described.

D. Diagnosis.

1. History.
   a. Obtain age; history of cardiac, respiratory, and neurologic diseases; medications; activities precipitating submersion (i.e., boating, diving, or ingestion of drugs/alcohol); duration of submersion; and temperature and type of water.

2. Physical examination.
   a. Tachypnea is the most common sign. Tachycardia is also common. Use a hypothermia thermometer; use of a standard thermometer can underestimate hypothermia and may cause premature stopping of CPR.
   b. Examination done to uncover injuries that were caused by or resulted from submersion.
   c. Neurologic classification.
      i. Category A: alert within 1 hour of presentation. These patients do well.
      ii. Category B: obtunded and stuporous but arousable at evaluation. Most of these patients survive, and permanent neurologic deficits are rare.
      iii. Category C: comatose/abnormal respirations/abnormal response to pain. High mortality and survivors have high rate of neurologic dysfunction.
3. Laboratory studies.
   Obtain hemoglobin, hematocrit, electrolytes, arterial blood gas analysis, blood alcohol level, prothrombin time/partial thromboplastin time, serum creatinine, urinalysis, drug screen, cervical spine films, a chest radiograph, and an electrocardiogram.

E. Treatment.

1. Initial resuscitation.
   a. Mouth-to-mouth resuscitation should be started in the water.
   b. Carefully support the victim's neck to prevent exacerbation of vertebral injuries.
   c. Full CPR should begin immediately on shore. The traditional "airway–breathing–circulation" sequence is recommended for drowning victims, over the most recent "circulation–airway–breathing" approach.
   d. Resuscitation must be continued at least until the patient has been rewarmed.
   e. Remove wet clothing and begin external rewarming plus heated O_2 in the field. Target temperature for victims of cardiac arrest is between 32°C and 34°C.
   f. Cardiopulmonary bypass should be used in severe cases on arrival at the trauma center.
2. Therapy of underlying cause
   a. Administration of necessary antidotes or other measures.
   b. Anticonvulsant levels in known epileptic patients.
   c. Neck immobilization until C-spine cleared for possible head/neck trauma.
   d. Correct hypoglycemia and severe electrolyte abnormalities.
3. Treatment of respiratory and other organ failure.
   a. Administer oxygen for hypoxemia.
   b. Manage ARDS per conventional protocols. Low tidal volume ventilation is essential.
   c. Optimize fluid status and renal blood flow. Severe cases may require dialysis.
   d. Correct cardiac dysrhythmias by rewarming.

4. Neurologic therapy: Recommendations of the World Congress on Drowning are as follows:
   a. Restoration of circulation is the top priority.
   b. Therapeutic hypothermia to a core temperature of 32°C to 34°C should be maintained for 12 to 24 hours for survivors of cardiac arrest from drowning.
   c. Hyperthermia should be prevented at all times in the acute recovery period.
   d. Monitor for seizures and initiate treatment immediately as necessary.
   e. Blood glucose concentrations should be monitored frequently and normoglycemia maintained.
   f. Hypoxemia should be avoided.
   g. Hypotension should be avoided.

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47 Pulmonary Hypertension in the Intensive Care Unit

Ana Cojocaru and Kimberly A. Fisher

I. INTRODUCTION

A. Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure (mPAP) > 25 mm Hg, is a common finding in critically ill patients.

B. Decompensated right heart failure due to PH and requiring ICU admission is associated with a high mortality rate (32% to 41%).

II. CLASSIFICATION/ETIOLOGY

A. Classification: PH is classified into five groups based on similar pathology and response to treatment (Table 47-1). Grouping is based on the location of the primary abnormality.

B. Common etiologies of PH in the intensive care unit (Table 47-2).

1. Related to underlying critical illness.
- **a.** Acute respiratory distress syndrome (ARDS).
  - **i.** Reported in 93% to 100% of patients with severe ARDS.
  - **ii.** Usually mild to moderate severity; 7% with ARDS have severe PH.
  - **iii.** Severity of PH correlates with degree of lung injury.
  - **iv.** Incidence of PH may have decreased with low tidal volume ventilation.
- **b.** Acute pulmonary embolism.
  - **i.** Fifty percent obstruction of pulmonary vasculature must occur before PH occurs.
  - **ii.** PH may occur with lesser degree of pulmonary vascular obstruction in patients with underlying cardiopulmonary disease.

2. Decompensation of preexisting condition.
- **a.** Left-sided heart failure.
- **b.** Exacerbation of chronic hypoxemic lung disease (chronic obstructive pulmonary disease [COPD] or interstitial lung disease [ILD]).

3. Deterioration of chronic pulmonary arterial hypertension (PAH).

III. PHYSIOLOGY OF THE PULMONARY CIRCULATION AND RIGHT VENTRICLE

A. Normal pulmonary circulation.

1. Low-pressure and low-resistance vascular bed.

TABLE 47-1 Updated Clinical Classification of Pulmonary Hypertension

Group 1: pulmonary arterial hypertension (PAH)
Idiopathic PAH (IPAH)
Heritable
Drug and toxin induced
Associated with connective tissues disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis, chronic hemolytic anemia
Persistent pulmonary hypertension of the newborn
Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis

Group 2: pulmonary hypertension owing to left heart disease
Systolic dysfunction
Diastolic dysfunction
Valvular disease

Group 3: pulmonary hypertension owing to lung disease and/or hypoxia
Chronic obstructive pulmonary disease (COPD)
Interstitial lung disease (ILD)
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities

Group 4: chronic thromboembolic pulmonary hypertension (CTEPH)

Group 5: pulmonary hypertension with unclear multifactorial mechanisms
Hematologic disorders: myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Modified from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–S54.

2. Accommodates increases in cardiac output via dilatation and recruitment of previously closed vessels.
3. Thin-walled right ventricle (RV) able to accommodate large increases in volume (preload).

B. RV pressure overload.

1. Increases in afterload due to PH lead to proportionate decrease in RV stroke volume.
2. Decreased RV stroke volume reduces blood return to the left ventricle (LV), leading to decreased cardiac output.

TABLE 47-2 Common Causes of Pulmonary Hypertension in the Intensive Care Unit

Hypoxemia/parenchymal lung disease
Acute respiratory distress syndrome
Pulmonary embolism
Interstitial lung disease
Obstructive sleep apnea
Chronic obstructive pulmonary disease

Left heart disease
Acute myocardial infarction
Valvular disease (mitral regurgitation/mitral stenosis)
Severe diastolic dysfunction
Cardiomyopathy

Postoperative states
Coronary artery bypass grafting
Cardiac transplantation
Lung/heart–lung transplantation
Pneumonectomy

Thromboembolic lung disease
Pulmonary embolism

Deterioration of chronic pulmonary arterial hypertension
Infection
Fluid overloaded state
Arrhythmias
Pulmonary embolism
Acute on chronic pulmonary hypertension
Medication withdrawal

Modified from Zamanian RT, Haddad F, Doyle RL, et al. Management strategies for patients with pulmonary hypertension in the intensive care unit. *Crit Care Med* 2007;35:2037–2050.

3. Elevated RV end-diastolic pressure causes bowing of the interventricular septum toward the LV during diastole, preventing LV diastolic filling and further reducing cardiac output ("ventricular interdependence").
4. Can open foramen ovale, causing hypoxemia due to right to left shunting of blood.

IV. DIAGNOSIS

A. Signs and symptoms.

1. Symptoms may be related to
   a. PH: exertional dyspnea, fatigue, chest pain, palpitations, exertional syncope.

b. RV failure: peripheral edema, abdominal distension.
c. LV failure (pulmonary venous hypertension): orthopnea, paroxysmal nocturnal dyspnea.

2. Examination findings.
a. Elevated pulmonary artery pressure (PAP): prominent pulmonic component of second heart sound (P2), RV heave, early systolic ejection click, midsystolic ejection murmur, RV S4 gallop, prominent jugular "A" wave, holosystolic murmur along left lower sternal border.
b. RV failure: elevated jugular venous pressure, pulsatile hepatomegaly, peripheral edema, ascites, hypotension.

3. Non-PAH: Signs and symptoms of the underlying primary disease predominate—wheezing, decreased breath sounds, prolonged expiratory phase (COPD), crackles (ILD), and pulmonic bruits (chronic thromboembolic pulmonary hypertension).

B. Diagnostic testing.

1. Electrocardiography (ECG): not sufficiently sensitive to be used as screening tool.
a. Right axis deviation: occurs in 79% of patients.
b. Right atrial enlargement (P wave ≥ 2.5 mm).
c. Right ventricular hypertrophy (frontal plane QRS axis ≥ 80 degrees, R wave/S wave ratio in lead V1 > 1, R wave in lead V1 > 0.5 mV): occurs in 87% of patients.

2. Radiographic findings.
a. Enlarged main and hilar pulmonary arterial shadows (≥18 mm diameter in men, ≥16 mm in women).
b. Peripheral pulmonary vascular attenuation ("pruning").
c. RV enlargement with decreased size of the retrosternal clear space.
d. Radiographic findings may suggest underlying cause for PH: hyperinflation (COPD), prominent interstitial markings (ILD), cephalization and Kerley B lines (left-sided congestive heart failure).

3. Laboratory evaluation.
a. Evaluate for diseases associated with PH: HIV serology, antinuclear antibody, rheumatoid factor titers.
b. Brain natriuretic peptide (BNP) has prognostic significance for patients with PAH but of unclear clinical significance in patients with PH due to critical illness.

4. Transthoracic Doppler echocardiography (DE).
a. Role of DE in diagnosing PH.
i. Provides noninvasive estimate of PAP.
ii. Assesses RV and LV morphology and function.
iii. Excludes congenital heart disease, mitral valve disease, and left atrial myxoma.
iv. Follows changes after introduction of therapy.
b. Echocardiographic findings of PH include RV dilatation and hypertrophy, D-shaped LV, RV hypokinesis, tricuspid regurgitation, right atrial enlargement, dilated inferior vena cava (IVC).

TABLE 47-3 Right Heart Catheterization Findings Based on Etiology of Pulmonary Hypertension

Etiology of PH	PAP	PAOP	PAD–PAOP gradient	PVR
PAH, PH due to hypoxemic lung disease, CTEPH	Elevated	Normal	Elevated	Elevated
Pulmonary venous hypertension	Elevated	Elevated	Normal	Normal
Pulmonary venous hypertension with "active" component	Elevated	Elevated	Elevated	Elevated

c. DE estimates of PAP correlate well with invasively measured PAP in patients with left-sided heart failure, but, in patients with suspected PAH or underlying lung disease, DE can be inaccurate with a 30% to 40% false-positive rate.

5. Right heart catheterization.

a. Gold standard for diagnosis of PH, based on mPAP > 25 mm Hg.

b. Can differentiate pre- or postcapillary etiology of PH, based on PA diastolic pressure (PAD) to pulmonary artery occlusion pressure (PAOP) gradient (PAD–PAOP gradient, normal < 5 mm Hg) and calculation of pulmonary vascular resistance (PVR) (Table 47-3).

c. Prognostic value in patients with IPAH, mPAP ≥ 85 mm Hg, right atrial pressure ≥ 20 mm Hg, and cardiac index < 2 L/min/m^2 associated with increased mortality.

d. Assess pulmonary vasoreactivity.

i. Use short-acting pulmonary vasodilator (prostacyclin, adenosine, nitric oxide).

ii. Defined as 20% decline in PVR and mPAP by at least 10 mm Hg to <40 mm Hg with preserved or increased cardiac output (CO).

iii. Vasodilator responsiveness in patient with IPAH is predictive of long-term response to high-dose calcium channel blockers and suggests better prognosis.

iv. Clinical significance of vasoreactivity in other forms of PH is unproven.

6. Other studies.

a. Computerized tomography may be helpful in further delineating underlying parenchymal disease.

b. Ventilation–perfusion lung scan ($\dot{V}/\dot{Q}$ scan).

i. Test of choice for chronic thromboembolic pulmonary hypertension (CTEPH); normal or low-probability $\dot{V}/\dot{Q}$ scan virtually excludes CTEPH.

ii. Limited utility in critically ill patients as cannot be performed on intubated patients and may be difficult to obtain in unstable patients.

c. Computerized tomographic angiography can identify acute pulmonary emboli and often CTEPH, although its role in diagnosing CTEPH remains poorly defined.

V. TREATMENT

A. General measures.

1. Oxygen, to keep $Sao_2 \geq 90\%$.
2. Diuretics if patient has right heart failure and volume overload.
3. Maintenance of sinus rhythm if atrial fibrillation present.
4. Anticoagulation.
a. Possible survival benefit in patients with IPAH based on retrospective and nonrandomized prospective studies.
b. No proven role for anticoagulation for critically ill patients with nongroup 1 or group 4 forms of PH.

B. Pulmonary vasodilator therapy (reserved for patients with group 1 PAH).

1. Treatment with pulmonary vasodilators (prostacyclins, endothelin receptor antagonists, phosphodiesterase 5 inhibitors) of benefit for patients with PAH.
2. Choice of initial therapy in stable outpatients dictated by risk profile as assessed by functional class, 6-minute walk distance, BNP level, hemodynamic measure, and echocardiographic findings.
3. Epoprostenol (intravenous) is the only medication with proven survival benefit and therefore indicated for treatment of decompensated RV failure due to PAH.
a. Administration.
i. Typically initiated in intensive care unit with RHC in place.
ii. Start at dose of 1 to 2 ng/kg/min and uptitrate by 1 to 2 ng/kg/min at intervals of 15 to 30 minutes for hemodynamic goal of increased CO decreased PAP and PVR.
iii. Dose escalation limited by side effects (headache, jaw pain, nausea, diarrhea, systemic hypotension).
b. Complications.
i. Pulmonary edema (can be due to pulmonary venoocclusive disease, pulmonary capillary hemangiomatosis, or occult diastolic dysfunction).
ii. Hypoxemia due to nonselective pulmonary vasodilation with resultant shunting especially in setting of focal lung disease.
iii. Thrombocytopenia.
iv. Abrupt discontinuation leads to rebound PH and can cause death.
v. Catheter-associated infection or thrombosis.

C. Nongroup 1 PH.

1. Treatment of underlying disease: diuresis (group 2), adequate oxygenation (group 3), pulmonary thromboendarterectomy (group 4).
2. ARDS: no role for pulmonary vasodilators.
a. Intravenous pulmonary vasodilators increase intrapulmonary shunting with worsened oxygenation, no improvement in survival.

b. Inhaled pulmonary vasodilators (iNO, nebulized prostacyclin) improve oxygenation without improving survival.

D. ICU-specific considerations.

1. Vasopressors: limited data to guide choice of vasopressors in PH associated RV failure.
- **a.** Beneficial hemodynamic effects (reduced mPAP/PVR, preserved or improved cardiac output) with dopamine, dobutamine, and isoproterenol.
  - **i.** Dopamine and dobutamine use both associated with increased mortality but may reflect use in patients with more severe disease rather than direct deleterious effect on survival.
  - **ii.** Isoproterenol: beneficial effects offset by induction of tachyarrhythmias.
- **b.** Adverse hemodynamic effects (increased mPAP/PVR, stable or worsened cardiac output) with norepinephrine, phenylephrine, and vasopressin (high doses) and should therefore be avoided.

2. Mechanical ventilation.
- **a.** Hemodynamic effects of mechanical ventilation on PAP and RV.
  - **i.** Increased RV afterload, decreased RV preload; may be of less clinical importance at lower tidal volumes.
  - **ii.** Permissive hypercapnia increases mPAP and PVR, with decreased RV ejection fraction.
  - **iii.** Positive end-expiratory pressure (PEEP) increases PAP and PVR.
- **b.** Goals of mechanical ventilation in patients with PAH and RV failure include low tidal volume and low PEEP while avoiding permissive hypercapnia.

3. Surgical management: atrial septostomy.
- **a.** Decompresses RV and increases left atrial filling.
- **b.** Complicated by oxygen desaturation, associated with high morbidity and mortality in critically ill patients.
- **c.** Contraindications: RAP > 20 mm Hg, significant hypoxemia, PVR index > 4,400 dynes sec m^2/cm^5.

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48 Pleural Disease in the Critically Ill Patient

Andres F. Sosa, Crescens Pellecchia, and Mark M. Wilson

I. PLEURAL EFFUSIONS

A. General principles.

1. Pleural disease itself is an unusual cause for admission to the intensive care unit (ICU).
2. Exceptions are a large hemothorax for monitoring the rate of bleeding and hemodynamic status, an unstable pneumothorax (PTX), and a massive unilateral or bilateral pleural effusion causing acute respiratory failure.
3. Early recognition of an empyema is crucial.

B. Etiology.

1. Pleural effusions may be due to an imbalance of hydrostatic and oncotic pressures, capillary permeability changes, impaired lymphatic drainage, loss of lung volume (atelectasis), or combinations of these.
2. Congestive heart failure (CHF) is the most common cause of all pleural effusions, most of which are bilateral.
3. Hepatic hydrothorax occurs in 6% of patients with liver cirrhosis and clinical ascites.
4. Parapneumonic effusions due to community-acquired and nosocomial pneumonia are common in critically ill patients.
5. If pus is aspirated at thoracentesis or the Gram stain shows bacteria, the diagnosis of empyema is established, and immediate drainage is needed.
6. Other frequent causes of pleural effusion in the ICU include pancreatitis, pulmonary embolism, hypoalbuminemia, hemothorax, and postsurgical (cardiothoracic or abdominal) effusions. Esophageal rupture (elevated salivary amylase in pleural fluid) is an unusual but potentially life-threatening event requiring immediate diagnosis and therapy.

C. Pathophysiology.

1. Atelectasis causes pleural fluid by decreasing local pleural pressure; this creates a vacuum in the pleural space leading to extravasation of transudative fluid.
2. Hepatic hydrothorax results from movement of ascitic fluid through congenital or acquired diaphragmatic defects.
3. Pleural effusions from pancreatitis result from direct irritation of the diaphragm, extravasation of enzymes into the pleural space (pancreatic duct leaks), or fistulous tracts.

4. Effusions from pulmonary emboli result from increased capillary permeability, imbalance in microvascular and pleural hydrostatic pressures, and pleuropulmonary hemorrhage.
5. Pleural effusion, with or without PTX, occurs in 75% of cases of esophageal rupture.
6. Hemothoraces (fluid with a pleural fluid-to-blood hematocrit ratio >50%) warrant complete drainage.

D. Diagnosis.

1. Pleural effusions appear on supine CXR as increased homogeneous densities over the lower lung fields compared with the upper lung fields.
2. With hepatic hydrothorax, the CXR usually reveals a normal cardiac silhouette and a right-sided pleural effusion in 70% of patients. The fluid is transudative.
3. Parapneumonic effusions are commonly ipsilateral to a new infiltrate or consolidated lobe.
4. Effusions from pancreatitis are usually small and left sided (60%) but may be isolated to the right (30%) or bilateral (10%). The fluid is an exudate with amylase values greater than that of serum.
5. Pulmonary emboli usually produce exudative effusions; however, 20% are transudates.
6. A presumptive diagnosis of esophageal rupture requires immediate confirmation with contrast esophagrams. Amylase of salivary origin appears in pleural fluid in high concentration. The pH falls rapidly and progressively approaches 6.00.

E. Treatment.

1. Thoracentesis should be performed if the diagnosis is in question or if the patient's course is other than expected (patient is febrile or has pleuritic pain or unilateral or disparate-sized effusions).
2. Thoracentesis under ultrasonographic guidance has improved success rates and reduced the frequency of complications.
3. Therapeutic thoracenteses are primarily indicated for the relief of dyspnea.
4. Therapy for effusions due to CHF involves decreasing venous hypertension and improving cardiac output with preload and afterload reduction.
5. Treatment of hepatic hydrothorax is directed at resolution of the ascites with sodium restriction and diuretics. Chemical pleurodesis is often unsuccessful. Prolonged chest tube drainage is to be avoided due to an increased risk for infection, malnutrition, immunosuppression, and renal failure. This group of patients should be evaluated for a transjugular intrahepatic portosystemic shunt (TIPS) procedure.
6. When a parapneumonic effusion is free flowing on lateral decubitus CXR and thoracentesis shows a nonpurulent, polymorphonuclear neutrophil–predominant exudate with a fluid pH > 7.30, the patient has a high likelihood of resolution without sequelae over 7 to 14 days using antibiotics alone.
7. Draining the pleural space should be considered if the fluid is purulent, has a positive Gram stain or culture, or has indicators of a complicated effusion (fluid pH < 7.20, glucose < 60 mg/dL, or lactate dehydrogenase

(LDH) > 1,000 international units) given the associated increase in morbidity and mortality.

8. No specific therapy is usually necessary for effusions due to pancreatitis, unless hemorrhagic or complicated.
9. The diagnosis of spontaneous esophageal rupture dictates immediate intervention; survival is >90% if primary closure and drainage occurs within the first 24 hours.
10. Traumatic hemothorax should be treated with immediate tube thoracostomy.

F. Complications.

1. Absolute contraindications for thoracentesis include an uncorrectable bleeding diathesis or an uncooperative patient; the major relative contraindications are the presence of a small amount of pleural fluid and a low benefit-to-risk ratio for the procedure.
2. The risk of PTX with thoracentesis is inversely correlated with operator experience and minimized with the use of ultrasound.
3. In experienced hands, PTX is no more likely to occur in the patient receiving mechanical ventilation than in the patient who is not; however, if a PTX does develop, the patient receiving mechanical ventilation is at high risk of developing a tension PTX.
4. Complications resulting from diagnostic or therapeutic thoracentesis are similar. There is, however, an increased risk of PTX with a therapeutic procedure, and three complications unique to therapeutic thoracentesis may be seen—hypoxemia; reexpansion pulmonary edema; and hypovolemia.

II. PNEUMOTHORAX

A. General principles.

1. PTX refers to the presence of air in the pleural space.

B. Etiology.

1. Spontaneous PTX occurs without an obvious cause, either without findings of lung disease (primary spontaneous PTX or PSP) or with clinically manifest lung disease (secondary spontaneous PTX or SSP) such as chronic obstructive pulmonary disease, interstitial lung disease, *Pneumocystis jiroveci pneumonia*, necrotizing pneumonia, or cystic fibrosis.
2. Traumatic PTX results from penetrating or blunt chest trauma.
3. Iatrogenic PTX, the most common cause of PTX in the ICU, is a consequence of barotrauma associated with mechanical ventilation or invasive procedures (thoracentesis, central venous catheters).
4. PTX occurs in up to 8% of all patients with acute lung injury receiving mechanical ventilation.

C. Pathophysiology.

1. If the pressure gradient between the airways and pleural space is transiently increased, alveolar rupture may occur; air enters the interstitial tissues of the lung and may then enter the pleural space or decompress to the mediastinum and subcutaneous tissues.

2. When PTX occurs, the elasticity of the lung causes it to collapse until the pleural defect seals or the pleural and alveolar pressures equalize.
3. Progressive accumulation of air (and positive pressure) within the pleural space produces a tension PTX. Tension PTX compresses mediastinal structures, impairing venous return to the heart, decreasing cardiac output, leading to hypotension, and can cause fatal cardiovascular collapse. In the setting of mechanical ventilation, 30% to 97% of patients with PTX develop tension.

D. Diagnosis.

1. Most iatrogenic PTXs occur at the time of the procedure from direct lung puncture, but delayed (up to 12 to 24 hours later) PTXs have been noted.
2. In the supine patient, PTX gas accumulates anteriorly and, on CXR, outlines the anterior pleural reflection, the costophrenic sulcus (deep sulcus sign), and the anterolateral border of the mediastinum. The base, lateral chest wall, and juxtacardiac areas should be carefully visualized for evidence of PTX. Up to 30% of PTXs may not be detected initially, and half of these will subsequently progress to tension PTX.
3. PTX in the mechanically ventilated patient usually presents as an acute cardiopulmonary emergency with a mortality rate of 7% if it is rapidly diagnosed clinically versus a mortality rate of 31% to 77% when diagnosis is delayed.
4. The most common CXR signs of a PTX under tension are contralateral mediastinal shift, ipsilateral diaphragmatic depression, and ipsilateral chest wall expansion.
5. Pneumothorax can also be reliably diagnosed by bedside ultrasound when done by an experienced operator.

E. Treatment.

1. A first episode of PSP may be treated by simple drainage; SSP may need pleurodesis due to its high recurrence rates.
2. Up to half of spontaneously breathing patients with needle-puncture (iatrogenic) PTX may be managed expectantly without the need for tube drainage.
3. If the patient is receiving mechanical ventilation or if the PTX is large (>2 cm from chest wall at level of the hilum) or has caused substantial symptoms or gas exchange abnormalities, then tube thoracostomy should be performed as soon as possible. Treatment should not be delayed to obtain CXR confirmation. If a chest tube is not immediately available, placement of a large-bore needle into the anterior second intercostal space on the suspected side can be lifesaving.
4. Providing 100% oxygen may result in a fourfold increase in the mean rate of reabsorption of a pneumothorax.
5. The presence of a bronchopleural fistula on mechanical ventilation may rapidly lead to tension pneumothorax. Immediate placement of a chest tube is crucial. The chest tube should be of a caliber large enough to allow for proper decompression, meaning that larger tubes may be needed for bigger air leaks. To prevent loss of tidal volume from a large fistula, an effort must be made to reduce the gradient of pressure between

the airway and the pleural space; this may be achieved by minimizing suctioning, using low positive end expiratory pressure (PEEP), lowering tidal volumes and respiratory rates, and shortening inspiratory times.

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49 Mechanical Ventilation: Invasive and Noninvasive

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I. GENERAL PRINCIPLES. Indications for mechanical ventilation (MV) include hypoxic and hypercapnic respiratory failure. Intrinsic lung disease can result in hypoxemia and/or pump failure manifested by hypercapnia and hypoxemia. Pure hypercapnic respiratory failure can result from central nervous system (CNS) depression, respiratory muscle fatigue or weakness due to peripheral nervous system disease or an intrinsic muscle disorder, chest wall mechanical defects, and mediators of diseases that affect respiratory muscles (e.g., sepsis). Positive-pressure MV is currently the predominant means of providing ventilatory support, as opposed to negative-pressure ventilation. MV may be invasive (delivered through an endotracheal tube [ETT] or tracheostomy tube) or noninvasive positive-pressure ventilation (NIPPV) (delivered to the patient through a full-face or nasal mask).

A. Modes of invasive MV.

1. **Volume-cycled MV:** delivers a guaranteed preset volume (Vt) with each breath that is specified by the operator. Peak inspiratory pressures (PIPs) generated by the ventilator are variable with each breath, depending on airway resistance or compliance. A "pop-off" pressure is assigned to prevent excessive peak pressures that abort the breath when that pressure limit is reached. The time that it takes to deliver the Vt (inspiratory time or Ti) is also controlled by the operator because it is dependent on the volume, inspiratory flow rate ($\dot{V}i$), and waveform characteristics (square or decelerating waveforms), which are all specified by the operator.
   a. **Assist control (AC):** All breaths are assisted. The patient initiates a breath and a set inspiratory flow and Vt are delivered with each breath. However, if the patient's intrinsic rate falls below the preset basal rate, then all the breaths delivered are control breaths, spaced at regular time intervals. AC is also a time-triggered mode that delivers a preset volume if the patient does not initiate any spontaneous breaths. During the control and assisted breaths, the Vt and inspiratory flow and characteristics are exactly the same with each breath.
      i. Advantages include that a guaranteed Vt will be delivered, and when patients are in synchrony with the ventilator, this mode allows for minimal patient effort and rest for fatigued respiratory muscles.
      ii. Disadvantages include the following: The potential for induced respiratory alkalosis in patients with high respiratory drive (e.g.,

liver failure), patient asynchrony and respiratory muscle fatigue can occur, and I:E ratio can vary because the variable respiratory rate (RR) can alter the expiratory phase.

b. Synchronized intermittent mandatory ventilation (SIMV): SIMV can deliver three kinds of breaths—spontaneous, assisted, and mandatory breath. If no breaths are initiated within a period of time, a mandatory breath will be delivered. If the machine senses that the patient has taken a spontaneous breath just before the mandatory breath, the machine will recycle and then wait for the next spontaneous breath and assist it.

i. Advantages include an insured minimum $\dot{V}_E$ and backup rates for patients with apneas.

ii. Disadvantages include the following: The least beneficial mode for weaning, I:E ratio cannot be fully controlled given the variability in RR and presence of spontaneous breaths, and it does not provide the same degree of respiratory muscle rest as AC mode.

2. Pressure-limited MV delivers a flow until a preset pressure limit that is set by the operator is reached. PIP is therefore always the same as the sum of the preset pressure limit for each breath and the positive end-expiratory pressure (PEEP) value. Vt is variable with each breath, according to airway resistance and compliance.

a. Pressure support (PS): Every breath is an assisted breath. Each breath is triggered by the patient's respiratory effort. The patient determines the inspiratory flow rate and shape of the waveform as well as the RR. When a preset pressure limit is reached, inspiratory flow slows to <0.5 L/min and the machine cycles off.

i. Advantages include the following: better patient synchrony, it limits PIP, and probably is as effective as spontaneous breathing trial weaning.

ii. Disadvantages include the following: Apnea backup breaths are infrequent and less responsive than the backup from AC, inadequate volumes could be delivered if the ETT is blocked, and decreased lung compliance can cause preset pressure limit to stop inspiratory flow before an adequate Vt is delivered; asynchrony can occur due to high inspiratory pressure settings, low respiratory drive, and airflow obstruction with dynamic hyperinflation and with air leaks.

b. Pressure control (PC): PC is similar to AC in that control breaths are delivered at a preset time interval but with a preset pressure limit rather than a preset volume. RR and time to maximal pressure limit are both operator set, and spontaneous breaths can be interspersed between the mandatory breaths.

i. Advantages include the following: It limits PIP and plateau pressure (Pplat) to minimize barotrauma and it can control or extend Ti for inverse ratio ventilation (IRV) to increase mean airway pressure (MAP) and augment oxygenation.

ii. Disadvantages include the following: It cannot ensure minimal $\dot{V}_E$ with airway obstruction or poor compliance, sedation with

or without paralysis is necessary for IRV (I:E > 2:1), extended inspiratory time with circuit leaks, and exaggeration of inspiratory time can limit time for passive exhalation and contribute to autoPEEP.

c. **Bilevel:** a form of pressure-support ventilation that allows for unrestricted spontaneous breathing that switches between a high and low airway pressure based on an adjustable time sequence. Cycling between the two pressure settings can be synchronized with the patient's spontaneous breathing to maximize the I-pressure during inspiration and the E-pressure during expiration.
   i. Potential advantage is that it is theoretically more comfortable to the patient, resulting in less agitation and less need for sedation.
   ii. Potential disadvantages include that it is not well studied and safety has not been well established.

d. **Airway pressure release ventilation (APRV):** an extreme form of bilevel ventilation, maintaining a long period of high pressure followed by a very short period of low pressure (the "release"). This results in an inverse I:E ratio of 8 to 9:1. It is a time-triggered, pressure-limited, time-cycled mode that also allows for the patient to have spontaneous breathing.
   i. Potential advantages include that it may improve oxygenation in patients with severe ARDS, decreases the frequency of opening and closing of alveoli, limits the amount of alveolar stretching factors thought to promote lung injury, and decreases airway pressures.
   ii. Potential disadvantages are that it is not well studied, safety not established, and a high number of pneumothoraces in small studies.

e. High-frequency oscillation ventilation (HFOV): HFOV is a mode of ventilation that delivers very low Vt at very high RR, with RR typically set between 180 and 600 breaths per minute. Oxygen reaches the alveoli by diffusion, while exhalation is an active process. HFOV should only be used by critical care personnel with knowledge and experience with this mode of ventilation.
   i. Potential advantages include the possibility to improve oxygenation for patients with severe ARDS and that it may be beneficial in patients with bronchopleural fistulae.
   ii. Potential disadvantages include high risk for barotrauma, hypotension due to high intrathoracic pressures, need for sedation and paralysis, limited ability to interrupt ventilation for suctioning or moving patients without significantly worsening oxygenation, and limited studies demonstrating significant benefit over other forms of MV.

3. **Continuous positive airway pressure (CPAP)** occurs when the inspiratory and expiratory limbs are pressurized to a preset end-expiratory pressure. CPAP functions primarily as an oxygenation, upper airway soft tissue opening, and weaning modality.
   a. No inspiratory flow is delivered. The patient assumes most of the work of breathing (WOB) by generating his or her own RR, $\dot{V}i$, Vt, and therefore $\dot{V}_E$, closely simulating unassisted spontaneous breathing.

b. WOB is reduced compared to complete discontinuation from the MV circuit and delivery of only FIO_2 ("T piece"). Application of PEEP stents the airways open and allows for better exhaled Vt. CPAP can be used in coordination with flow-by. Flow-by occurs when a stream of gas is delivered across the ventilator circuit, assisting the patient in drawing his or her own $\dot{V}i$ and Vt.

i. Expiratory positive airway pressure (EPAP): Only the expiratory phase is pressurized. Compared to CPAP, EPAP has a lower MAP and higher WOB.

ii. For those dependent on MV for only oxygenation and not ventilation, CPAP can improve oxygenation without subjecting the patient to the harmful effects of MV.

B. Ventilator settings for invasive positive-pressure MV.

1. **Fraction of inspired oxygen (FIO_2):** Supplemental oxygen is adjusted to target an oxygen saturation (SaO_2) > 90% and/or PaO_2 > 60 mm Hg. O_2 should not be withheld for any concern of CO_2 narcosis on MV. O_2 should not be withheld for concern of toxicity, if required. It is believed that clinically significant O_2 toxicity is unlikely to occur with FIO_2 < 0.6 even with prolonged delivery.
2. **Tidal volume (Vt)** is constant in volume-cycled modes and varies with each breath in pressure-limited modes. In patients without lung disease, Vt of 8 mL/kg of ideal body weight is used provided the Pplats remain <30 cm H_2O. Lower tidal volumes are recommended for ARDS of 6 mL/kg of ideal body weight. Vt ≤ 8 mL/kg is recommended in patients with obstructive lung disease (asthma, COPD). Limiting Vt decreases expiratory time (Te) and minimizes autoPEEP.
3. **Inflation pressure limit:** High inflation pressures cause barotrauma. Increased Pplat (end-inspiratory airway plateau pressure), rather than PIP, is most injurious, reflecting alveolar overdistension and not airway resistance. No threshold is safe but Pplat ≤ 30 cm H_2O is recommended. Use of sedation with or without paralytics can decrease dynamic hyperinflation and allow for lower Pplat. MV pop-off pressure should be set approximately 10 cm above the PIP.
4. **Respiratory rate:** RR and Vt determine $\dot{V}_E$. For SIMV and PC modes, RR is preset and rates of 12 to 20 breaths per minute are reasonable. The AC rate is set below the patient's spontaneous RR to minimize the chance of controlling ventilation with its attendant risk of respiratory muscle atrophy. RR and/or Vt should be adjusted down for autoPEEP and for patients with chronic hypercapnia to avoid posthypercapnic metabolic alkalosis.
5. **Sensitivity:** This adjustment affects the amount of drop in airway pressure that is required before the ventilator senses the patient's effort and assists them during AC and PS. Sensitivities of approximately 0.5 to 1 cm H_2O allow very weak patients to initiate a breath. When the patient is making an effort to breathe and the machine is not triggering in assisted modes, consider whether the sensitivity value is too high and needs to be reduced or autoPEEP is present and the applied PEEP should be increased.

6. **Minute ventilation ($\dot{V}_E$):** $\dot{V}_E$ is the product of the Vt and RR. Normal individuals maintain normocapnia with a resting $\dot{V}_E$ of approximately 5 L/minute. Adjustment of $\dot{V}_E$ is based on $PaCO_2$ as a marker of ventilatory requirements. "Permissive hypercapnia" is employed in ARDS and status asthmaticus to minimize the risk of barotrauma. Most experts do not recommend administering buffer solutions unless the pH is <7.15. Permissive hypercapnia is felt to be contraindicated in patients with increased intracranial pressure. Overventilating patients with chronic CO_2 retention is to be avoided because it can lead to posthypercapnic metabolic alkalosis. High ventilatory requirements are present in hypermetabolic states (sepsis) or high caloric intake where excess CO_2 production needs to be eliminated. High dead space also increases ventilatory requirements for the same CO_2 target.
7. **Inspiratory flow rate ($\dot{V}i$):** Inspiratory flow is usually specified rather than I:E ratio (except in PC mode). The ratio of Vt (liters) to $\dot{V}i$ (L/minute) determines Ti (minute). Because RR determines total respiratory cycle time and exhalation is passive, I:E ratio is determined by the above mentioned three fixed parameters.
   a. For volume-cycled modes, Ti will be longer and PIP lower for a decelerating waveform and mimics PS mode. Delivering volumes with decelerating flows tends to promote recruitment and may reduce risk of barotrauma. Higher $\dot{V}i$ decreases Ti to allow for greater time for passive exhalation and reduce autoPEEP in obstructive lung diseases. Higher $\dot{V}i$ increases PIP but should not affect Pplat. However, there is a theoretic concern that too-rapid lung inflation can cause "deformation injury."
   b. In PS mode, patients determine their own $\dot{V}i$. $\dot{V}i$ is specified for PC ventilation in that one can determine how quickly to achieve the pressure limit.
   c. In asthma and COPD, the expiratory time needs to be lengthened to allow for adequate exhalation of trapped gas. Therefore, the I:E ratio needs to be as low as possible, achieved by a low RR, a short inspiratory time, a lower Vt, or higher inspiratory flow rates.
8. **Inspiratory hold and IRV:** No flows are delivered, but passive exhalation is prevented. Ti is regulated in PC mode to precisely control I:E ratio, tantamount to an "inspiratory hold." It is used to recruit collapsed lung units in ALI and increase Pao_2, as an alternative to increasing PEEP, which increases Pplat and risks barotrauma. IRV occurs when Ti is greater than Te and is used in severe ARDS to treat hypoxemia refractory to other ventilatory measures.
9. **Mean airway pressure:** MAP is the airway pressure averaged over the entire respiratory cycle time, inspiration, and exhalation. Attention to MAP is important in ALI in treating hypoxemia because more time in inspiration, keeping the lung inflated with an inspiratory hold, increases the oxygen driving pressure. An inspiratory hold or IRV, increasing Vt and RR, increases the time spent in inhalation and therefore the amount of time in positive pressure. Increasing PEEP and thereby exhalation phase pressure increases MAP.

10. **Positive end-expiratory pressure:** PEEP is the maintenance of positive pressure after expiratory flow is completed until the next inspiratory flow is initiated.
    a. Applied PEEP distends airways down to the alveoli to allow for more complete exhalation and CO_2 removal by reducing air trapping. PEEP improves $\dot{V}/\dot{Q}$ matching, by stenting open alveoli with patent capillaries. It helps distribute alveolar debris and decreases O_2 diffusion distance but does not drive fluid out of the lung.
    b. Intrinsic PEEP (PEEPi) or autoPEEP is the positive pressure that occurs from incomplete exhalation before the initiation of the next breath. Dynamic hyperinflation causes a pressure gradient and a persistent flow. PEEPi is detected on the flow versus time curve when expiratory flow does not return to baseline before the next inhalation. Also, if the end-expiratory airway Pplat is greater than applied PEEP, then PEEPi is present.
    c. Applied PEEP usually ranges between 0 and 20 cm H_2O and is usually adjusted up or down in 2.5- to 5-cm H_2O increments.
    d. In obstructive diseases, applied PEEP can mitigate the effects of PEEPi in spontaneously breathing patients.
    e. Complications of excessively applied or intrinsic PEEP include overdistension, barotrauma, hypotension from limiting venous return, and decrease in left ventricular diastolic compliance due to lung hyperinflation compressing the lateral cardiac wall.
    f. When applied prospectively, a low PEEP strategy yielded the same outcomes as the high PEEP strategy. Therefore, the lowest possible PEEP that promotes adequate oxygenation, in conjunction with other ventilatory strategies, is recommended.
11. **Recruitment maneuvers** occur when an expiratory hold is applied with high PEEP levels for an extended time to increase Pao_2 by opening collapsed lung units. There are also no data that show that recruitment maneuvers affect outcomes in ARDS.

C. NIPPV refers to the delivery of ventilatory support without placement of an ETT or tracheostomy. While most modes of ventilation can be administered noninvasively, bilevel is the most commonly used. Bilevel is a pressure-limited mode in which inspiratory positive airway pressure (IPAP) and EPAP are set. Bilevel positive-pressure ventilation allows for patient triggering, and most machines have a backup-rate mode that allows for both spontaneous and timed delivered ventilations. IPAP is similar to PSV and augments ventilation, while EPAP is similar to PEEP and augments oxygenation. It usually takes no more than 1 to 2 hours to determine if the patients will respond appropriately and sufficiently to this form of ventilation.

1. **Ventilator interfaces:** Several interfaces are available when using NIPPV, such as full-face masks, nasal masks, and nasal pillows. In patients with respiratory failure, full-face masks have been shown to be the most effective but are the least comfortable. Masks must fit tight to prevent leakage of air. Facial hair, NG tubes, lack of teeth, and craniofacial abnormalities may result in poorly fitting masks.

2. **Patient selection:** Ideal candidates for NIPPV are patients with acute respiratory failure, the etiology of which can be corrected or improved in 24 to 36 hours, and who are more awake and can protect their airway from aspiration and clear airway secretions by coughing.
   a. Patients likely to fail NIPPV include those who are uncooperative, agitated, or anxious and those with excess secretions, increased age, poorly fitting masks, and severe hypercapnic respiratory failure defined as pH < 7.10 and $Paco_2$ > 92.
   b. Contraindications to NIPPV include respiratory or cardiac arrest, severe encephalopathy (GCS < 10), increased intracranial pressure, hemodynamic instability, and facial trauma.
3. **Disease states.**
   a. Disease states most likely to benefit include acute COPD exacerbation, cardiogenic pulmonary edema, acute asthma exacerbation, and noncardiogenic pulmonary edema from fluid overload (e.g., renal failure).
   b. Disease states less likely to benefit include severe pneumonia, ARDS, and conditions unlikely to improve in 24 to 36 hours.
4. Potential benefits include decreased need for invasive ventilation, decreased length of ICU and hospital stay, and decreased incidence of nosocomial infections (sinusitis, ventilator-associated pneumonia [VAP]).
5. Potential disadvantages include inability to feed patients, limited use to no more than 24 to 36 hours continuously, and that up to 50% of patients do not tolerate or benefit from NIPPV.

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50 Mechanical Ventilation: Discontinuation

Scott E. Kopec and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Outcome for patients with respiratory failure.

1. Mechanical ventilation (MV) can be discontinued in 80% to 90% of patients within 3 weeks. Of this group, 77% can be extubated within 72 hours of the start of MV.

2. Ten to twenty percent require prolonged MV > 21 days. Weaning from MV in this group may take >3 months. One-year survival can be as high as 93%. Survivor quality of life may be minimally to moderately impaired when assessed 2 years later.

B. Four potentially reversible causes of prolonged MV.

1. Inadequate respiratory drive due to
- **a.** Nutritional deficiencies.
- **b.** Sedatives.
- **c.** Central nervous system (CNS) abnormalities.
- **d.** Sleep deprivation.

2. Inability of the lungs to carry out gas exchange without MV if the underlying cause of respiratory failure has not significantly improved.

3. Inspiratory respiratory muscle fatigue or weakness due to
- **a.** CNS and neuromuscular diseases or dysfunction.
- **b.** Active inflammatory processes (e.g., sepsis).
- **c.** Nutritional and metabolic deficiencies.
- **d.** Medications (e.g., corticosteroids).
- **e.** Chronic renal failure.
- **f.** Increased work of breathing (WOB) from intrinsic lung disease or extravascular lung water, chest wall disorders, or cardiovascular failure
- **g.** Hypoxia and hypercapnia.

4. Psychological dependency.

C. Pump failure from inspiratory respiratory muscle fatigue is probably the primary etiology for failure of discontinuation of MV in most patients on prolonged MV.

II. INDICATIONS

A. When to initiate discontinuation trials.

No objective data exist on when to begin the weaning process, so clinical judgment is necessary. A monitored spontaneous breathing (SB) screening trial is recommended when the following criteria are met.

1. The underlying reason for MV has been stabilized, and the patient is improving.
2. Hemodynamically stable and on no or minimal and unchanging doses of pressors.
3. Adequate oxygenation ($Pao_2/Fio_2 > 200$, positive end-expiratory pressure [PEEP] < 7.5 cm H_2O, $Fio_2 < 0.5$).
4. The patient is able to initiate spontaneous inspiratory effort.

B. Principles of weaning.

1. Breathing is a form of continuous muscular exercise, and MV discontinuation should reflect principles of muscle training that include stressing respiratory muscles to early fatigue and then resting them. Maintain a structured, progressive program because benefit is transient.
2. Sudden increased WOB with MV discontinuation can cause harmful effects. Monitor closely during the first 5 minutes and return to MV if there is deterioration.
3. Because physiologic failure can cause tachycardia, tachypnea, and hypertension as can anxiety, do not assume anxiety alone is the cause.
4. Screening patients daily may reduce intensive care unit (ICU) stay and time of MV.
5. Studies have shown that when a standardized, hospital-based protocol is used that incorporates a team approach between physicians, nurses, and respiratory therapists, success rates for weaning are significantly improved.

C. Predictive indices for successful discontinuation.

1. It does not appear that any single parameter can consistently and accurately predict success in weaning. The following parameters have the highest accuracy.
   a. Spontaneous respiratory rate (RR) < 38 breaths per minute (sensitivity 88%, specificity 47%).
   b. Rapid shallow breathing index (RSBI) < 100 breaths/min/L. RSBI is the RR divided by tidal volume (Vt) in liters averaged over 1 minute. RSBI should be measured while the patient is breathing spontaneously.
      i. RSBI < 100 has a PPV of 0.78 and NPV of 0.95.
   c. Maximal inspiratory pressure (MIP) less than 15 cm H_2O had a negative predictive value of 100%.
2. The above predictive results for successful discontinuation of MV are even less accurate the longer a patient is dependent on MV.
3. Clinical observation of respiratory muscles is not reliable in predicting failure. Both muscle fatigue and any increase in respiratory muscle load cause a change in rate, depth, and pattern of breathing. Nevertheless, close monitoring is necessary because discontinuation failure is inevitable if these signs are due to fatigue. If these signs never appear, successful discontinuation is likely.

III. PROCEDURE

A. Modes of discontinuation from MV.

Four modes of weaning are typically used: SB trial, synchronized intermittent mechanical ventilation (SIMV), pressure support (PS), and noninvasive positive-pressure ventilation (NIPPV). Successful discontinuation of MV is less determined by the mode of weaning than by identification and correction of medical barriers to weaning. However, when compared to other modes, SIMV has nearly consistently performed the worst in clinical trials and is not recommended.

1. **SB discontinuation trial.**
   - **a.** Sudden, complete withdrawal of machine-supported breaths.
   - **b.** Only one SB trial is recommended in a 24-hour period.
   - **c.** A "T piece" is attached to the endotracheal tube (ETT) to deliver humidified oxygen for the SB trial. T-tube flow should exceed the patient's inspiratory flow requirement.
   - **d.** SB trial can also be performed using continuous positive airway pressure (CPAP), typically set at a pressure of 5 cm H_2O through the ventilator.
   - **e.** The CPAP trial allows for the monitoring of RR, minute ventilation ($\dot{V}_E$), and Vt during weaning.
   - **f.** Arranging for a sedation holiday starting approximately 1 hour before starting the SB trial has been shown to improve the success of the weaning trial.
2. **Pressure support ventilation discontinuation trial.**
   - **a.** Gradual decrease of augmented inspired pressure so that the patient gradually assumes the WOB.
   - **b.** A major adverse effect of PS discontinuation trials is PS-induced central apneas.
3. **Noninvasive positive-pressure ventilation (NPPV) weaning.**
   - **a.** The first approach is to extubate directly to NPPV once screening and predictive indices suggest that weaning is close but not likely successful in the short term.
   - **b.** The second uses NPPV as a bridge to avoid reintubation after discontinuation from MV has failed. In this setting, mortality may actually be worse.

B. When to extubate.

1. Most patients who have well-tolerated SB trials lasting 30 to 120 minutes can be considered for extubation.
2. For patients being weaned on PS mode, extubation can be considered after the patient tolerates PS of 5 to 7 cm H_2O for 2 hours.
3. Patients with the following conditions should probably have well-tolerated trials lasting >2 hours before considering extubation.
   - **a.** On prolonged MV (>21 days).
   - **b.** Neurologic patients who are predicted to have difficulty clearing their airway secretions.
   - **c.** Patients who have failed recent extubations.

C. Failed extubation.

1. The two most common causes of failed extubations are upper airway obstruction and inability to protect the airway and clear secretions.
2. Risk factors for upper airway obstruction include:
   a. Prolonged MV.
   b. Female sex.
   c. Repeated or traumatic intubations.
3. The cuff-leak test does not consistently predict clinically significant upper airway obstruction.
4. Patients at high risk for postextubation upper airway obstruction should be considered for extubation in a well-equipped setting such as an operating room environment, be extubated over an ETT exchange catheter, and/or have a helium–oxygen tank and reintubation equipment at the bedside.
5. Pretreating patients at high risk for postextubation upper airway obstruction with 40 mg of methylprednisolone 4 hours before extubation or 20 mg every 4 to 6 hours 12 to 24 hours before extubation might be beneficial in decreasing the rate of postextubation stridor and the need for reintubation.
6. Predictors for patients failing extubation due to inability to protect the airway and clear secretions include:
   a. Cough peak flow measurements of <60 L/minute.
   b. Secretion volume of ≥2.5 mL/hour.
   c. Poor mentation, as defined by the inability to perform the following commands:
      i. Open eyes.
      ii. Follow the observer with eyes.
      iii. Grasp hand.
      iv. Stick out tongue.

D. Recommended SB discontinuation protocol.

The salient features are as follows:

1. Sit the patient in an upright position.
2. Avoid sedation unless anxiety is overwhelming and a barrier to weaning.
3. "T piece" with humidified oxygen at inspiratory flow rates to match inspiratory requirements or keep patient connected to the ventilator and use CPAP mode and 5 cm H_2O.
4. Continue the trial unless clinical findings, judgment, oxygenation, and cardiac monitoring suggest respiratory muscle fatigue or clinical deterioration with the following parameters.
   a. Clinical criteria of diaphoresis and increased respiratory effort, paradoxical breathing, or use of accessory respiratory muscles are present.
   b. Heart rate >30 beats per minute over baseline, profound bradycardia, ventricular ectopy, or supraventricular tachyarrhythmias.
   c. Mean arterial blood pressure >15 mm Hg or <30 mm Hg from baseline.
   d. RR > 35 breaths per minute for at least 5 minutes, Sao_2 < 90%, or dyspnea rated by the patient as >5/10.
   e. Routine arterial blood gas (ABG) analysis is not thought necessary in all cases, because blood gas alterations may be a late finding in respiratory muscle fatigue.

5. When the trial is terminated due to failure, resume the prior MV settings.
6. Once-a-day SB trials are recommended over other modes.

D. Managing discontinuation failure.

1. The respiratory muscles are pivotal in the onset and perpetuation of respiratory failure.
2. Interventions to increase respiratory muscle strength.
   a. Reverse malnutrition.
   b. Correct electrolyte abnormalities (PO_4^-, Mg^{+2}, Ca^{+2}, K^+).
   c. Correct hypoxemia.
   d. Correct chronic hypercapnia during MV.
   e. Reverse hypothyroidism.
   f. Maximize cardiovascular function.
   g. Minimize sedation unless anxiety is overwhelming and inhibiting weaning.
   h. Consider the use of progesterone 20 mg TID as a respiratory center stimulant in patients with few or no spontaneous breaths when off sedation.
   i. Consider and evaluate for the possibility of myopathy and polyneuropathy.
   j. Treat sleep deprivation and central fatigue with short-acting sedatives at night.
   k. Improve diaphragmatic function by sitting the patient up during weaning.
   l. Mobilize patient as tolerated with early physical therapy.
   m. Consider using theophylline to stimulate the respiratory center and augment diaphragmatic contraction and suppress its fatigue. Avoid drug interactions with calcium channel blockers that could inhibit the beneficial effects on the diaphragm.
3. Interventions to decrease respiratory muscle demand.
   a. Maximize treatment of systemic disease to decrease metabolic requirements and mitigate cytokine production that can adversely affect muscle function.
   b. Prescribe bronchodilators and discontinue β-blockers for increased airway resistance when not needed for comorbid diseases.
   c. Give a course of systemic corticosteroids in exacerbations of chronic obstructive pulmonary disease (COPD) and asthma.
   d. Prescribe diuretics to reduce pulmonary edema or states of fluid overload.
   e. Routinely evaluate and treat cardiac dysfunction including myocardial ischemia.
   f. Consider replacing the ETT with a larger one (≥8-mm internal diameter).
   g. Add CPAP for marginal cardiac function to decrease left ventricular preload.
   h. Determine whether the ventilator is increasing WOB, whether the sensitivity or trigger threshold is appropriate, and whether the inspiratory flow rate or pattern matches patient demand.

i. Avoid hyperinflation, apply extrinsic PEEP in the presence of inspiratory triggering threshold load from intrinsic PEEP, and consider the type of humidification devices because dead space and airway resistance are increased with heat and moisture exchangers rather than heated humidifiers.

j. Evaluate overfeeding causing increased CO_2 production in chronic hypercapnic patients and the need for increased alveolar ventilation to remove this excess product of metabolism. Overfeeding may precipitate respiratory acidosis or ongoing respiratory muscle fatigue in patients unable to increase alveolar ventilation adequately. Increased total calories, rather than percentage carbohydrates, are the more likely cause of the increased CO_2 production.

4. Potential advantages of tracheostomy for prolonged failure to wean patients.

a. Studies have not demonstrated that tracheostomy preformed at 7 days leads to better outcomes than at 14 days.

b. Potential advantages of a tracheostomy.

i. More stable means of ventilating and allows for greater flexibility to perform CPAP or SB trails with a tracheostomy mask.

ii. Decrease WOB by decreasing air flow resistance.

iii. Improved patient comfort with potential need for less sedation medication.

iv. Allowing the patient to have better communication.

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51 Respiratory Adjunct Therapy and Noninvasive Respiratory Monitoring

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I. AEROSOL THERAPY

A. General principles.

1. Allows direct delivery to airways and lungs, which allows more rapid onset of action, lower doses, and fewer nonpulmonary side effects than systemic administration.

B. Medications and indications.

1. Aerosols of sterile water or saline theoretically humidify inspired gas, hydrate dry mucosal surfaces, and enhance expectoration.
   a. Three percent hypertonic saline may be beneficial for pulmonary toilet.
   b. Data support routine use of 7% hypertonic saline only in cystic fibrosis (CF).
2. Mucolytic agents are designed to facilitate expectoration of secretions.
   a. Aerosolized *N*-acetylcysteine (Mucomyst) has low efficacy, may induce bronchospasm, and has been shown to be ineffective in chronic obstructive pulmonary disease (COPD) and CF.
   b. Recombinant human DNAse may be helpful in CF.
3. Aerosolized antimicrobials have a limited role in treating acute infections.
   a. Inhaled tobramycin is indicated for CF when the patient is at least 6 years old, has forced expiratory volume (FEV1) 25% to 75% predicted, and is colonized with *Pseudomonas aeruginosa*.
   b. In limited studies in non-CF bronchiectasis, inhaled tobramycin may decrease the sputum bacterial density in patients with pseudomonal infections.
   c. Inhaled pentamidine is second-line agent for *Pneumocystis* (*P. jiroveci*) pneumonia prophylaxis.
   d. Inhaled ribavirin does not have a well-established role in treating respiratory syncytial virus (RSV), severe acute respiratory syndrome (SARS), or influenza A and B infections.
4. Racemic epinephrine decreases laryngeal edema by causing vasoconstriction, but its effectiveness in treating epiglottitis and postextubation stridor is unclear.
   a. Adults: 0.5 mL of 2.25% solution in 3-mL normal saline every 4 to 6 hours.

b. Side effects of racemic epinephrine include rebound laryngeal edema and cardiac side effects (tachycardia and angina); therefore, mixtures of helium and oxygen (heliox) appear to be a less toxic option for treating these airway emergencies.

5. Bronchodilators.

a. Inhalation of short-acting β_2-selective adrenergic agonists (e.g., albuterol, pirbuterol) is first-line therapy for treating asthma and COPD exacerbations.

b. Long-acting inhaled β_2-selective adrenergic agonists are currently not recommended as treatment for acute exacerbations of asthma or COPD.

c. Inhaled albuterol can acutely but transiently lower serum potassium levels.

d. Inhaled anticholinergics (e.g., ipratropium bromide) have a role in treating acute asthma in the emergency department when combined with short-acting β_2-selective adrenergic agonists, may prevent bradycardia during suctioning when intubated, and may be useful in severe bronchorrhea.

6. Inhaled corticosteroids are used to prevent exacerbations of asthma and COPD.

a. Delivered by metered-dose inhaler (MDI) or dry powder inhaler.

b. No established role during acute exacerbations of obstructive lung disease.

7. Others.

a. Inhaled cyclosporine may improve survival in lung transplant patients.

b. Inhaled iloprost, a prostacyclin analog, is available for the treatment of primary pulmonary hypertension and pulmonary hypertension associated with connective tissues disease, appetite suppressants, and chronic thromboembolic disease.

i. Doses of 2.5 to 5 μg are administered six to nine times a day through the Prodose Adaptive Aerosol Delivery (AAD) nebulizer system (Respironics, Murrysville, PA).

C. Procedure.

1. Nebulizers.

a. Air-jet nebulizers are a nonpropellant-based option with no superiority compared to MDI with spacer use and appropriate patient technique.

b. Recommended when patient cannot coordinate use of MDI or the drug is not available as MDI.

2. MDIs.

a. Pressurized canister that contains drug suspended in propellant, typically hydrofluoroalkane (HFA).

b. Delivery dependent on technique that requires slow, deep inhalation followed by a breath hold of approximately 10 seconds.

c. Effectiveness improved by spacer and holding chamber.

3. Dry powder aerosols.

a. Available for β-adrenergic agonists and corticosteroids.

II. LUNG EXPANSION TECHNIQUES

A. General principles: Lung expansion techniques aim to resolve and prevent atelectasis.

B. Indications: to prevent atelectasis and reduce pneumonia risk by providing periodic hyperinflations.

C. Procedure: Techniques include coached sustained maximal inspiration with cough, incentive spirometry, volume-oriented intermittent positive-pressure breathing, intermittent continuous positive airway pressure (CPAP), or positive expiratory pressure mask therapy.

III. AIRWAY CLEARANCE

A. General principles: Mucociliary clearance and cough are mechanisms for clearing respiratory secretions that can be augmented therapeutically.

B. Treatment.

1. Mucociliary clearance can be enhanced with inhaled β-agonists or aminophylline.
2. Chest physical therapy includes therapeutic positioning and percussion and vibration of the chest wall but is not effective in patients with a weak cough.
   a. Indicated in CF, bronchiectasis, COPD when expectorates >30 mL of sputum/day, and lobar atelectasis.
3. Cough effectiveness may be improved by positive mechanical insufflation followed by manual compression of the lower thorax and abdomen in quadriparetic patients, an abdominal push maneuver in patients with spinal cord injuries, abdominal binding and muscle training of the clavicular portion of pectoralis major in tetraplegic patients, and chest physical therapy.
   a. Other techniques, with limited studies to support use, include the flutter valve mucus clearance device, positive expiratory pressure mask therapy, autogenic drainage, and cough mechanical assist device (insufflator/exsufflator).
4. Endotracheal suctioning, with preoxygenation with 100% oxygen, is used when an artificial airway is present. Nasotracheal suctioning is not recommended due to serious complications, including death. Nasopharyngeal suctioning is the preferred method for clearing the upper airway.

C. Postprocedure considerations.

1. Chest physical therapy is infrequently complicated by pulmonary hemorrhage, hypoxemia, rib fractures, increased intracranial pressure, decreased cardiac output, and increased airway obstruction.
2. Mechanical suctioning may be complicated by tissue trauma, laryngospasm, bronchospasm, hypoxemia, cardiac arrhythmias, respiratory and cardiac arrest, atelectasis, pneumonia, and misdirection of catheter and, rarely, may result in death.

IV. ADMINISTRATION OF MEDICAL GASES

A. Indications.

1. Oxygen therapy is indicated if Pa_{O_2} < 60 mm Hg, arterial saturation (Sa_{O_2}) < 90%, and in certain conditions: acute respiratory distress/failure (hypoxemic or hypercapnic), cardiac arrest or acute myocardial infarction, acute asthma, normoxemic hypoxia (e.g., carbon monoxide poisoning), hypotension, shock, severe trauma, preoperative and postoperative states, and cluster headaches.
2. Helium–oxygen mixtures (heliox) are indicated for upper airway obstruction (postextubation, tracheal tumors, or extrinsic compression), croup, and laryngeal edema; studies do not support routine use in acute asthma and bronchiolitis.
3. Nitric oxide, a potent pulmonary vasodilator, has been used, with questionable benefits, in acute respiratory distress syndrome (ARDS), pulmonary hypertension, status asthmaticus, acute sickle cell crisis, and right heart failure after cardiovascular surgery.
4. Hyperbaric oxygen therapy (100% oxygen at two to three times atmospheric pressure) is used to treat decompression sickness, arterial gas embolism, and severe carbon monoxide poisoning (see Chapters 52 and 129); it is used as adjunctive therapy in osteoradionecrosis, clostridial myonecrosis, and compromised skin grafts. It has not been shown to be beneficial in treating severe brain injury, acute cerebral vascular accidents, or for acute coronary syndromes.

B. Procedure.

1. Nasal cannulae deliver oxygen comfortably and allow for eating and talking. Oxygen can be delivered as either low-flow or high-flow oxygen.
   a. Low-flow oxygen delivers O_2 at rates typically between 0.5 and 4 L/minute. Flow rates of >2 L/minute should be humidified as higher rates can cause excess upper airway dryness. The fraction of inspired O_2 (F_{IO_2}) delivered to the patient can vary, depending on the patient's RR and Vt. Flow rates of 0.5 to 1.0 L/minute approximate an F_{IO_2} of 0.24; 2 L/minute approximates 0.28.
   b. High-flow oxygen delivers O_2 at rates up to 40 L/minute. Special devices (Vapotherm; Stevensville, Maryland) are used to heat and humidify the delivered O_2. High-flow O_2 delivered by nasal cannulae may be more comfortable for the patient than a face mask and may result in better oxygenation.
   c. The flow rates needed to deliver O_2 by nasal cannulae can be decreased using a reservoir device, such as an Oxymizer or Oxymizer Pendant. The reservoir stores O_2 and this allows for the lower flow rate. These devices are most beneficial in patients requiring >4 L/minute flow rates.
2. Masks can be uncomfortable, require removal for eating, and should be used cautiously in sedated, obtunded, or restrained patients.
   a. Deliver F_{IO_2} of 0.35 to 0.50 with flow rates of at least 5 L/minute or greater (to avoid rebreathing CO_2 from mask's reservoir).
   b. Venturi masks deliver oxygen most accurately and up to F_{IO_2} of 0.50.
   c. Nonrebreathing and partial rebreathing oxygen masks with reservoir bags can deliver high F_{IO_2} (>0.50) when oxygen flows are 8 to 10 L/minute.

3. Transtracheal catheters deliver O_2 directly into the trachea via a minitracheostomy. Patients with transtracheal catheters should be cared for by providers with experience in this form of O_2 delivery. If a patient develops respiratory distress while using one of these devices, one must be urgently concerned for the possibility of airway obstruction due to mucous balls forming at the tip of the catheter.
4. In the hypercapnic–hypoxemic patient, therapy should begin with F_{IO_2} of 0.24 or 0.28 by nasal cannula or mask, increasing supplemental oxygen incrementally and assessing for hypercarbia. An initial increase in P_{aCO_2} of 5 to 10 mm Hg is expected and should not deter delivery of oxygen to maintain a $P_{aO_2} \geq 60$ mm Hg.
5. Heliox mixtures should contain a minimum of 40% helium to be effective.

C. Postprocedure considerations.

1. In hypercapnea, supplemental oxygen can sometimes worsen hypercarbia, leading to CO_2 narcosis.
2. Abruptly discontinuing oxygen when hypercapnea occurs can excessively lower P_{aO_2}.
3. Complications of oxygen therapy are decreased mucociliary clearance, tracheobronchitis, and pulmonary oxygen toxicity. $F_{IO_2} > 0.50$ should be restricted, whenever possible, to <48 hours.

V. NASAL CPAP

A. General principles.

1. Nasal CPAP applies CPAP during the respiratory cycle. Bilevel continuous positive airway pressure (BiPAP) allows independent adjustments of inspiratory and expiratory pressures.
2. CPAP splints the upper airway in obstructive sleep apnea.

B. Indications.

1. Nasal CPAP is used to treat obstructive sleep apnea/hypopnea syndrome, chronic left ventricular failure, and Cheyne-Stokes respirations.
2. See Chapter 49 for a discussion of noninvasive positive-pressure ventilation (NIPPV).

C. Procedure.

1. Patients usually respond to 3- to 15-cm H_2O of nasal CPAP by an optimally fitting nasal or full-face mask.

D. Postprocedure considerations.

1. Different masks and levels of BiPAP may be tried to improve tolerance.

VI. COMMUNICATION ALTERNATIVES

A. General principles: Speech requires air flow through the vocal cords.
B. Indications: Patients with tracheostomy tubes and need for speech.

C. Procedure.

1. Ventilator dependent.
   - **a.** Partial cuff deflation techniques, though not routinely performed, require close monitoring and ventilator adjustments.
   - **b.** One-way, positive-closure, no-leak valve (e.g., Passy-Muir valve; Irvine, California) should be used only with a fully deflated tracheostomy cuff and close ventilator monitoring and adjustments; it should not routinely be used while on a ventilator. Contraindications include inflated cuff, tracheal/laryngeal obstruction, excessive secretions, laryngectomy, bilateral vocal cord paralysis, unconsciousness, or unstable condition.
   - **c.** Talking tracheostomy tube (Trach-Talk, Portex, Inc.) can be used for whispered speech.
   - **d.** Computer-assisted communication is another option.
2. Nonventilator dependent.
   - **a.** Deflation of the tracheostomy cuff (or a cuffless tube) with intermittent gloved finger occlusion.
   - **b.** One-way, positive-closure, no-leak valve (e.g., Passy-Muir valve) attached to a cuffless or deflated tracheostomy tube.
   - **c.** For postlaryngectomy patients, consider electronic larynx and Blom-Singer tracheostoma valve for prosthesis-assisted tracheoesophageal speech.

D. Postprocedure considerations.

1. Deflating the cuff during mechanical ventilation may decrease gas delivery to the lungs. Closely monitor tidal volumes and gas exchange is recommended.
2. Use one-way valves only if the patient is conscious, is able to self-remove the valve or has someone in attendance who can do it in the event of sudden respiratory distress, and is able to clear secretions.
3. Some studies suggest increased risk of aspiration if oral feeds are given with a one-way valve in place.

VII. RESPIRATORY MONITORING

A. Respiratory rate is a predictor of outcome.

B. Respiratory impedance monitors measure respiratory rate and estimate tidal volumes but are poor detectors of apnea, are affected by movement, and have a false-positive alarm rate of approximately 30%.

C. Respiratory inductive plethysmography measures movement of chest and abdomen for evaluation of respiratory rate and tidal volume. It is more accurate than impedance monitors, but only two-thirds of the estimated tidal volumes are within 10% of actual tidal volumes.

D. Pulse oximetry measures hemoglobin saturation in tissue to derive the arterial saturation. Causes of poor signal detection: probe malposition, hypothermia, vasoconstriction, pulselessness, and dark skin. Causes of falsely low arterial saturations: nail polish, ambient light, methylene blue and other dyes, and elevated serum lipids. Causes of falsely high

arterial saturations: carboxyhemoglobin, methemoglobin, hypothermia, and ambient light.

E. Capnography measures of expired P_{CO_2}. End-tidal CO_2 is measured during the last 20% of exhalation. In the intensive care unit, capnography is most useful for detecting extubation, presence or absence of respiration, and return of spontaneous circulation after cardiac arrest. End-tidal CO_2 measurements are unreliable indicators of P_{aCO_2} in critically ill patients.

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52 Acute Inhalational Injury and Chemical and Biological Agents of Mass Destruction

Michael L. Barretti and Mark M. Wilson

I. GENERAL PRINCIPLES

A. Inhalational injuries may occur due to workplace exposures, natural disasters, or terrorist attacks and result in a variety of syndromes based on the chemical and physical properties of the toxicant involved and the intensity and duration of exposure.

B. Agents may be inhaled as gases, vapors, dust, fumes, or smoke.

C. Disease is caused by asphyxia, direct toxicity, or systemic reactions.

II. ASPHYXIANTS

A. General principles.

1. Simple asphyxiants include carbon dioxide (CO_2), methane, nitrogen (N_2), natural gas, propane, and acetylene.
2. Chemical asphyxiants are present in the atmosphere in minute amounts or are released by manufacturing processes or combustion; they asphyxiate at low concentration and include carbon monoxide (CO), hydrogen sulfide (H_2S), oxides of N_2, and hydrogen cyanide (HCN).

B. Etiology.

1. CO and CO_2, the most common asphyxiants, accumulate in sealed or poorly ventilated areas. They are generated during combustion of carbon-containing fuel.
2. HCN is used as inorganic salt in metallurgy, electroplating, and photo processing and in the combustion of N_2-containing polymers.

C. Pathophysiology.

1. Simple asphyxiants displace or dilute ambient oxygen (O_2) causing tissue hypoxia; chemical asphyxiants interfere directly with O_2 uptake, transport, or utilization.
2. The affinity of CO for hemoglobin is 240 times that of O_2. The formation of carboxyhemoglobin (COHgb) causes a reduction in the total O_2-carrying capacity of the blood, a left shift of the oxyhemoglobin dissociation curve, and an increased affinity for O_2 at the remaining binding sites. Because of the increased affinity of CO for fetal hemoglobin, infants and fetuses are at greater risk for poisoning.

3. The clinical effects of HCN and H_2S intoxications are directly related to inhibition of cellular respiration in the mitochondria and occur rapidly after inhalation.

D. Diagnosis.

1. Breathlessness, tachycardia, headache, fatigue, delirium, syncope, coma, and cardiac arrest may suggest exposure to asphyxiants; severity varies on duration of exposure and underlying health of the victim.
2. In CO poisoning, although arterial O_2 tension (Pao_2) is normal or near normal, measured O_2 saturation and content are reduced. Ordinary pulse oximetry is unable to distinguish which specific gas (CO vs. O_2) is bound to hemoglobin; therefore, the more specific co-oximetry is needed to measure COHgb levels. Signs and prognosis of acute poisoning correlate imprecisely with COHgb levels. Generally, levels <10% are usually not associated with symptoms; levels of 10% to 20% may be associated with headache, tinnitus, dizziness, nausea, and mild behavioral abnormalities; levels of 20% to 40% can present with coma and seizures; and levels >40% are associated with increased risk of cardiac arrest.
3. Both HCN and H_2S typically cause metabolic acidosis with an elevated anion gap, an elevated serum lactate, and a mixed venous O_2 saturation higher than normal.

E. Treatment.

1. The basic management for any asphyxiation scenario includes removal of the source, 100% O_2, and support of cardiorespiratory function.
2. O_2 is the major therapy for CO poisoning. It decreases the half-life of COHgb by competing with CO for hemoglobin binding sites. Patients with COHgb levels >25% (>20% if pregnant), loss of consciousness, and severe metabolic acidosis (pH < 7.10) or who have evidence of possible end-organ ischemia (e.g., electrocardiogram [ECG] changes, chest pain, altered mental status) are candidates for hyperbaric O_2 therapy (strength of recommendation is weak).
3. Treatment of HCN and H_2S is similar (see Section V). Sodium thiosulfate is not necessary for H_2S intoxication, however.

III. IRRITANT GASES

A. General principles.

1. Various agents act as toxic irritants to the respiratory tract and cause mucosal edema, impaired mucociliary function, and pulmonary edema with high-concentration exposures.
2. Agents in this class include ammonia (NH_3 and ammonium hydroxide in solution), chlorine (Cl_2), phosgene ($COCl_2$, which hydrolyzes to form hydrochloric acid [HCl]), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), formaldehyde, cadmium, mercury, and the metal hydrides.

B. Etiology.

1. NH_3 is found in fertilizer production, chemical, plastic, and dye manufacture.

2. Cl_2 is used in the production of alkali bleaches and disinfectants and in paper and textile processing. Most exposures result from industrial spills and loss of containment during transportation.
3. Firefighters, welders, and paint strippers are exposed to heated chlorinated hydrocarbons, and $COCl_2$ is released in these settings. Because $COCl_2$ is less irritating to the eyes and mucous membranes than Cl_2 or HCl and may be inhaled for prolonged periods without discomfort, the risk of serious injury to the lower respiratory tract is greatly increased.

C. Pathophysiology.

1. NH_3, SO_2, and HCl have high water solubility and tend to be highly irritating to conjunctivae, mucous membranes, and upper air passages. Laryngospasm, bronchospasm, and mucous membrane necrosis ensue.
2. Less water-soluble agents (oxides of N_2, $COCl_2$) can penetrate more deeply into the respiratory tree and can cause damage at the alveolar and lower airway levels, resulting in pulmonary edema and bronchospasm. The absence of immediate symptoms with these less water-soluble agents can prolong exposure.

D. Diagnosis.

1. These disorders usually occur during an industrial- or transport-related accident.
2. Patients present in acute respiratory distress with evidence of burn injury; skin lesions; intense edema, erythema, and ulceration of the conjunctival and mucous membranes; and possible laryngeal obstruction.
3. Auscultation of the chest may reveal stridor, crackles, and expiratory wheezing.
4. The typical bat's-wing distribution of cardiogenic pulmonary edema is less likely on chest radiograph (CXR) than patchy infiltrates.

E. Treatment.

1. Mainstay of management is removal from the site of exposure and immediate O_2.
2. Airway patency should be ensured because of the risk of progressive laryngeal edema over several hours. Bronchospasm is treated with bronchodilators.
3. Intravenous fluids to offset fluid losses from mucosal edema and sloughing from burns.
4. Empiric antibiotics are not indicated, and the early use of corticosteroids is controversial.

IV. SMOKE INHALATION

A. General principles.

1. Approximately 80% of fire-associated deaths are from smoke inhalational injury.
2. Inhalational injury has a greater effect on mortality than burn size or patient age.

B. Pathophysiology.

1. Respiratory injuries in fire victims with smoke inhalation can be the result of asphyxia, heat, and exposure to multiple toxic products of combustion (e.g., HCN, aldehydes, acrolein, dioxides of N_2 and sulfur, vaporized HCl).
2. Most deaths are the result of asphyxia, primarily due to CO intoxication.
3. Direct heat injury is usually limited to the upper respiratory tract. Edema formation and upper airway obstruction occur in up to 30% of burn patients and present 4 to 24 hours after exposure.
4. Smoke irritation can cause tracheobronchitis, severe bronchoconstriction, and frank pulmonary edema. Although pulmonary edema is rare (<10%), it is associated with high mortality rates (83%).

C. Diagnosis.

1. Classic predictors of smoke inhalation injury include a consistent exposure history; respiratory signs and symptoms (dyspnea, hoarseness, cough, chest discomfort, wheezing, stridor); cervical, facial, and oropharyngeal burns (especially between the nose and mouth); and expectoration of carbonaceous sputum.
2. Initial evaluation should focus on recognition and treatment of CO poisoning and airway obstruction, the major early problems. A delay in symptom onset (hours to days) is not uncommon. Lung examination and CXR may not be abnormal until 24 hours later.
3. COHgb levels >10% are markers of the potential for inhalation of other toxins. Unexplained metabolic acidosis or a lactate concentration >10 mM/L in the presence of normal or mildly elevated COHgb levels and normal Pao_2 suggests cyanide exposure.

D. Treatment.

1. Control of the airway is the initial priority. Immediate endotracheal intubation is indicated for stridor, facial burns, central nervous system, and depression or with evidence of upper or lower airway edema. Because airway edema evolves over time and intubation may become increasingly more difficult if it is delayed, all patients with significant smoke inhalation should have urgent laryngoscopy to assess the risk for airway compromise by monitoring the development of any oropharyngeal erythema, edema, or blistering of the mucosa.
2. Nasotracheal intubation may be preferred over orotracheal intubation in the presence of mouth burns.
3. All patients should be started on 100% humidified O_2. Nebulized β_2-agonists should be given to treat bronchospasm.
4. Consider hyperbaric O_2 therapy, if available, for CO intoxication (see Section II.E).
5. Methemoglobinemia, from oxidation of hemoglobin by cyanide, causes impaired O_2 binding and tissue delivery. It is treated with intravenous methylene blue.
6. Anecdotal evidence suggests that corticosteroids should be reserved for severe upper airway obstruction and bronchospasm resistant to bronchodilator therapy.

V. CHEMICAL AND BIOLOGICAL AGENTS OF MASS DESTRUCTION

A. General principles.

1. Chemical and biological agents can be used by terrorists against the general population or can be accidentally released. These include gases, liquids, or solids with direct toxic effects in relatively low concentrations.

B. Pathophysiology.

1. Chemical agents include (a) nerve agents (organophosphorous compounds that irreversibly inhibit acetylcholinesterase, most toxic) such as sarin and tabun, (b) vesicants ("blister agents") such as sulfur mustard and lewisite, (c) toxic asphyxiants such as cyanide, (d) lung irritants ($COCl_2$, Cl_2) that can cause acute lung injury, and (d) nonlethal, temporary incapacitating agents such as tear gas.
2. Biological agents that have the greatest potential to cause mass casualties (Category A agents) include anthrax, plague, smallpox, botulism, tularemia, and viral hemorrhagic fevers. Category B agents that have some potential for mass casualties include Q fever, brucellosis, staphylococcal enterotoxin B, ricin, and *Clostridium perfringens*.

C. Diagnosis.

1. A classic clue of a chemical weapon release is the rapid onset of symptoms in the context of mass casualties. Bioweapons release may take many hours or days to become apparent.
2. Nerve agent exposure results in excess cholinergic activity ("SLUDGE" syndrome of ***s***alivation, ***l***acrimation, ***u***rination, ***d***efecation, ***g***astric distress, ***e***mesis). Ventilatory failure is the primary cause of death.
3. Vesicants result in early development of sore throat, cough, and hoarseness followed by dyspnea, skin erythema, and eye irritation. Acute mortality is low; morbidity may be high.
4. Cyanide exposure results in tachypnea and tachycardia, followed by agitation, muscle weakness, seizures, and even the development of acute respiratory distress syndrome (ARDS) and cardiac arrest.
5. Pulmonary or "choking agents" hydrolyze with exposure to water to form HCl. Symptoms start with irritation of the eyes, nose, and airways and may progress to vomiting, headache, noncardiogenic pulmonary edema, and respiratory failure.
6. Smallpox (*Variola major*) is transmitted person to person by respiratory droplets. Clinical manifestations occur in distinct phases with a prodrome of high fevers, nausea/vomiting, and backache followed by a sequential rash (distinctly synchronous and centrifugal spreading lesions from face and hands to extremities and then the trunk over approximately 1 week). Patients are infectious until all crusts fall off. Disease is confirmed by analysis of skin scrapings, vesicular fluid, or oropharyngeal swabs. Strict containment procedures are required for agents such as smallpox that pose a high risk of aerosol-transmitted infection or life-threatening disease, and handling of all specimens requires a biosafety level 4 facility.
7. Anthrax (*Bacillus anthracis*) occurs in cutaneous, gastrointestinal, and inhalational forms based on route of entry of spores. The inhalational version

leads to fulminant respiratory failure, pleural effusions, hemorrhagic mediastinitis, and massive bacteremia. Organism is easily cultured from blood and other body fluids.

8. Plague (*Yersinia pestis*) is highly contagious from person to person and is rapidly fatal in the pneumonic form. Presenting features are fever/chills, dyspnea, chest pain, and cough with hemoptysis. Buboes are not always present.
9. Botulinum is an extremely potent toxin produced by *Clostridium botulinum* and may cause a life-threatening paralytic illness.
10. Ricin is a potent toxin that inhibits protein synthesis at the ribosome. It requires extraction from castor bean seeds. Inhalation may lead to airway necrosis, severe pulmonary edema, fibrinopurulent pneumonia, and mediastinal lymphadenitis. Ricin toxicity is not contagious to others.

D. Treatment.

1. The steps that need to be taken after a bioterrorist attack include detection, containment, rapid decontamination, prophylaxis, and direct treatment against the specific agent.
2. Removal of contaminated clothing can eliminate 80% to 90% of chemical contaminants.
3. For nerve agents: Administer O_2, atropine, pralidoxime, a benzodiazepine for any seizures, and supportive measures.
4. For cyanide: 100% O_2, intravenous hydroxocobalamin or sodium nitrite and sodium thiosulfate (specific antidotes), and supportive care.
5. There are no approved drugs for the treatment of smallpox. Strict airborne and contact isolation are necessary. Therapy is based on supportive care and vaccination at an early stage.
6. Prompt intravenous ciprofloxacin or doxycycline with clindamycin and/or rifampin is used for inhalational anthrax. All exposed cases should have 60 days of prophylaxis. Anthrax vaccine is not available to the general public at this time.
7. Traditionally, streptomycin or gentamicin is the mainstay of therapy for *Y. pestis*. Alternate antibiotics include ciprofloxacin or doxycycline. All individuals who come within 2 m of a patient with pneumonic plague should receive postexposure prophylaxis with doxycycline or ciprofloxacin. At this time, there is no approved vaccine against plague.
8. Treatment of botulism includes supportive care; mechanical ventilation, if necessary; and early administration of antitoxin.
9. Management of ricin exposure involves decontamination and general supportive care. There is no specific antidote available.

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53 Disorders of Temperature Control: Hypothermia

Jiaying Zhang, Susanne Muehlschlegel, and Mark M. Wilson

I. UNINTENTIONAL HYPOTHERMIA

A. General principles.

1. Hypothermia is defined as core temperature ≤ 35°C (95°F).
2. When body temperature decreases, the hypothalamus modulates autonomic tone causing cessation of sweat production, constriction of cutaneous vasculature, and increased heat production during the shivering phase (35°C to 30°C).
3. Temperature regulation declines with age as a result of deterioration in sensory afferent neurons, cortical function, and effector responses.

B. Etiology.

1. The most frequent causes of hypothermia are exposure to cold, use of certain drugs (alcohol, phenothiazines, barbiturates, neuroleptics, paralytics), and hypoglycemia.
2. Other common causes include hyperglycemia, hypothyroidism, adrenal insufficiency, central nervous system (CNS) disorders, extensive burns, sepsis, and trauma.

C. Pathogenesis.

1. The incidence of hypothermia doubles with every 5°C drop in ambient temperature. Wet clothing effectively loses up to 90% of its insulating value. Convective heat losses due to wind may increase losses to greater than five times baseline values.
2. Most sedative–hypnotic drugs cause hypothermia by inhibiting shivering and impairing capability for voluntary control of temperature.
3. Hypoglycemia lowers cerebral intracellular glucose concentrations and impairs hypothalamic function. In acute hypoglycemia, hypothermia occurs due to peripheral vasodilation and sweating.
4. Increasing degrees of hypothermia produce malignant dysrhythmias, depressed cardiac function, and hypotension. The electrocardiogram (ECG) in mild hypothermia shows bradycardia with prolongation of the PR interval, QRS complex, and QT interval. At temperatures <33°C, the ECG commonly shows a characteristic J-point elevation. At temperatures <30°C, first-degree block is common. Atrial fibrillation (AF) is extremely common at temperatures of 34°C to 25°C, and ventricular fibrillation (VF) is frequent at <28°C. Third-degree block and asystole are common when core temperatures drop to <20°C.

5. Pulmonary mechanics and gas exchange appear to change little with hypothermia. Both tidal volume and respiratory rate decline as core temperature lowers. At temperatures <24°C, respirations may cease.
6. As blood pressure decreases during the nonshivering phase (<30°C), renal blood flow may decrease by 75% to 85%, without a significant decrease in urine production. This process is termed *cold diuresis* and is due to a defect in tubular reabsorption. The net result is dehydration and a relatively hyperosmolar serum.
7. Hypothermia is neuroprotective; complete neurologic recovery has been described in hypothermic adults after 20 minutes of complete cardiac arrest and after up to 3.5 hours of cardiopulmonary resuscitation.
8. The white blood cell count in mild hypothermia remains normal to slightly elevated; it may drop severely at temperatures <28°C. The hematocrit usually rises in patients at a temperature of 30°C from dehydration and splenic contraction.
9. Hepatic dysfunction is common and involves synthetic and detoxification abnormalities. Ileus and pancreatitis can also occur.
10. Hypothermia directly suppresses the release of insulin and increases resistance to insulin's action in the tissues. Any hyperglycemia, however, is usually mild.
11. The hypothermic host is prone to infections secondary to impairment of immune function and decrease in inflammatory responses, secretion of cytokines, and suppression of leukocyte migration and the function of phagocytic cells.

D. Diagnosis.

1. Hypothermia is diagnosed by history of exposure, a high-risk patient profile (elderly, alcoholic, diabetic, quadriplegic, or severely debilitated), clinical examination, and laboratory abnormalities.
2. Cool skin, muscle rigidity, shivering or muscle tremor, and acrocyanosis are present in most noncomatose patients.
3. Between 35°C and 32°C, the patient may be verbally responsive but incoherent and between 32°C and 27°C, stuporous or confused, and at temperatures <27°C, most patients are comatose but respond purposefully to noxious stimuli. Deep coma is uncommon but, when present, may be difficult to distinguish from death. The criteria for death cannot be applied until core temperature is back near 37°C.
4. Thermometers calibrated to record temperatures <35°C should be used; only sites that reflect core temperature should be measured (bladder, rectal, tympanic, esophageal, or great vessel sites).

E. Treatment.

1. Treatment should be aggressive. Wet clothes should be removed and replaced with dry ones. The victim should be insulated from cold and wind. Rough handling must be avoided; even minor manipulations can induce VF.
2. Fluid resuscitation, preferably through a central vein, should be attempted in all patients in hypothermic shock. Slightly hypotonic crystalloid fluids should be given after warming to at least room temperature. Pressor agents and procedures (intubation or catheter placement) should not be withheld because of a fear of dysrhythmia.

3. Management of dysrhythmias must be approached in a nontraditional manner because many pharmacologic agents, pacing efforts, and defibrillation attempts do not work in the hypothermic patient. Because atrial dysrhythmias and heart block generally resolve spontaneously on rewarming, therapy is usually unnecessary. Digitalis should be avoided (efficacy is unclear and toxicity increases with rewarming); calcium channel blockers have not been shown to be efficacious. Both procainamide and lidocaine have been of little benefit. Bretylium appears to be the drug of choice and has been shown to both decrease the incidence of VF and increase the likelihood of successful cardioversion. Electrical defibrillation should probably be attempted at least once, but it is unlikely to succeed until the patient's core temperature >30°C.
4. P_{CO_2} and pH values uncorrected for temperature may be used accurately to assess these patients. However, because of a decrease in oxygen solubility on warming the arterial blood sample to 37°C, P_{O_2} values must be corrected for temperature or the presence of hypoxemia may be overlooked. To correct P_{O_2} values: For each degree that body temperature is <37°C, decrease the P_{O_2} measured at 37°C by 7.2%.
5. If hypoglycemia is present, the patient should be given 25 to 50 g of glucose as a 50% dextrose solution. Because of the ineffective action of insulin and the relatively high serum osmolarity from cold diuresis, treatment with highly concentrated glucose solutions should be delayed until the blood glucose level is measured.
6. Rewarming methods may be divided into three categories: passive external rewarming, active external rewarming, and active central rewarming. Passive external rewarming is the least invasive and slowest rewarming technique. It requires only that the patient be dry, sheltered from wind, and covered with blankets to decrease heat loss, thereby allowing thermogenesis to restore normal temperature. Temperature increase varies inversely with the patient's age; the average rate of temperature increase with this method is 0.38°C per hour.
7. Active external rewarming by use of warmed air circulated through a plastic blanket surrounding the patient (Bair Hugger) has proved safe and effective in rewarming postoperative patients and appears to work well with other types of hypothermia.
8. Active central rewarming is the fastest and most invasive warming technique available. Safe and effective methods include the following: oxygen that has been humidified and heated to 40°C to 46°C delivered by face mask or endotracheal tube (raises temperature slightly <1°C per hour), peritoneal lavage with saline or dialysate fluid heated to 38°C to 43°C and exchanged every 15 to 20 minutes (raises temperature by 2°C to 4°C per hour), and hemodialysis or cardiopulmonary bypass (raises temperature by 1°C to 2°C per hour).

II. THERAPEUTIC HYPOTHERMIA

A. General principles.

1. Therapeutic hypothermia (TH) is the intentional reduction of core body temperature to 32°C to 35°C (mild to moderate cooling).

B. Pathophysiology.

1. TH is the first treatment with proven neuroprotective efficacy by attenuating secondary injury after a primary neurologic insult.
2. This secondary injury phase evolves within hours and is characterized by the initiation of inflammatory response, activation of heat and cold shock proteins, vasogenic and cytotoxic edema, impaired brain metabolism, and apoptosis.
3. TH reduces cerebral metabolism, suppresses the inflammatory cascade that can lead to blood–brain barrier disruption, and preserves cell membrane integrity, thereby decreasing intracranial pressure–related complications.

C. Clinical application of therapeutic hypothermia.

1. Two sentinel multicenter, randomized controlled trials published in 2002 established firm evidence that TH improves survival and neurologic outcome after sudden cardiac arrest with a shockable rhythm (VF, pulseless ventricular tachycardia [VT]).
2. The American Heart Association recommends TH (32°C to 34°C for 12 to 24 hours) following resuscitation from out-of-hospital cardiac arrest with a shockable rhythm.
3. Hypothermia remains an experimental treatment with unknown clinical relevance for patients with out-of-hospital cardiac arrest with a nonshockable rhythm (asystole, pulseless electrical activity), ischemic or hemorrhagic stroke, traumatic brain injury, or acute spinal cord injury.
4. Patients with rapidly progressive acute liver failure are at high risk for developing cerebral edema and intracranial hypertension. TH has been shown in small reports to reduce cerebral edema in these patients, but randomized clinical trials are needed to confirm its efficacy.

D. Cooling methods.

1. The process of TH is divided into three phases: induction, maintenance, and rewarming.
2. During the induction phase, patients should be cooled as quickly as possible by using a combination of refrigerated saline infusions ([4°C] at 30 to 40 mL/kg), ice packs, surface cooling, or endovascular cooling.
3. Advantages of endovascular cooling include shorter time to target temperature and effective precise temperature control. Disadvantages include its invasive nature and potential increased risk of deep venous thrombosis, bacteremia, and sepsis.
4. During the maintenance phase, target temperature is tightly controlled (maximum fluctuations 0.2°C to 0.5°C). Attention should focus on maintaining adequate arterial perfusion pressure, normocarbia, perfusing rhythm, normal electrolyte levels, and glucose control. Surveillance and prophylactic treatments for potential sources of infection is necessary. Shivering should be aggressively treated with sedatives and possibly neuromuscular blockade. A detailed description of the physiologic changes and potential side effects of hypothermia is listed in Table 53-1.
5. The rewarming phase is associated with hemodynamic instability often referred to as the *postresuscitation syndrome*. Slow and controlled rewarming at rate of 0.2°C to 0.5°C per hour is preferred to minimize any rebound brain edema and hyperkalemia.

TABLE 53-1 Physiologic Changes and Potential Side Effects of Hypothermia

Temp	Effect	Cause	Treatment
<35.9°C	Sinus bradycardia	Likely due to decreased myocardial contractility	Consider isoproterenol, dopamine, or a pacing wire. Atropine not effective
	Hypovolemia	Due to cold diuresis	IV fluids, vasopressors, inotropic agents. Mechanical cardiac assistance if needed
	Impaired coagulation	Platelet dysfunction does not begin until temperature <35°C. Clotting factors are affected only with temperature <33°C, due to impaired liver function.	Coagulation test may not show abnormalities unless performed at the patient's actual core temperature. Active bleeding in polytrauma patients should be controlled before hypothermia is initiated.
	Infections	Impaired immune function and inflammatory responses	Pay specific attention to catheter insertion sites and surgical wounds. Consider surveillance cultures and antibiotic prophylaxis.
	Shivering	Increased sympathetic tone, brain attempts to generate shivering to abolish hypothermia	Magnesium IV; adequate sedation (propofol, benzodiazepines) and analgesia (meperidine, opiates); paralytics
	Increased drug levels and/or enhanced effect of the drug	Reduced liver enzyme activity, reduced liver perfusion, and reduced production of bile	Specific focus to sedation and analgesia; benzodiazepines and opiates can accumulate; use bolus doses rather than increasing continuous infusions.
	Hyperglycemia	Decreased insulin sensitivity and secretion	Increase insulin doses during induction, and decrease during rewarming.
	Electrolyte loss	Increased renal excretion	Repletion as needed
	(K^+, Mg^{++}, phos, Ca^{++})	(caused by cold diuresis and tubular dysfunction)	K^+ levels may rise during rewarming; slow rewarming can give time to the kidneys to excrete the excess K^+.
<30°C	Cardiac dysrhythmias: AF, VF, VT	Probable coronary vasoconstriction and coronary ischemia	Difficult; myocardium at deep hypothermia becomes less responsive to antiarrhythmic drugs and defibrillation.

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The full textbook chapter from which this Manual's summary is based.

54 Disorders of Temperature Control: Hyperthermia

Saef Izzy, Susanne Muehlschlegel, and Mark M. Wilson

I. HEAT STROKE

A. General principles.

1. Heat stroke is a syndrome of acute thermoregulatory failure in warm environments caused by increased heat production and/or impaired heat loss. It is characterized by central nervous system (CNS) depression, core temperatures over 40°C, and typical biochemical and physiologic abnormalities.
2. Mortality may reach 70%. About 4,000 deaths occur annually in the United States.

B. Etiology.

1. Exertional heat stroke is typically seen in active younger persons. With thermoregulatory mechanisms intact, it features rapid onset and high core temperatures.
2. Nonexertional ("classic") heat stroke affects predominantly elderly or sick persons. With some impairment of thermoregulatory control, it develops slowly over several days and presents with minimally elevated core temperatures.
3. Hypothalamic thermoregulation processes (peripheral vasodilatation, thermal sweating, and cardiac changes) are activated by core temperature increases of ≤1°C (1.8°F). Impaired cardiovascular status, damage to anterior group of hypothalamic nuclei, severe dehydration, and vasoconstricting medications (anticholinergics, diuretics, alcohol) can predispose.
4. Deficient voluntary control and poor acclimatization increase the risk when ambient temperatures are high.

C. Pathophysiology.

1. Direct cellular toxicity results from temperatures >42°C (the *critical thermal maximum*); mitochondrial activity and enzymatic reactions become dysfunctional, and there is destabilization of cell membrane integrity.
2. Metabolic changes: Dehydration, metabolic acidosis, and local hypoxia potentiate the damage from severe heat stress. Significant muscle enzyme elevation and rhabdomyolysis occur commonly in exertional but rarely in classic heat stroke. Hyperglycemia and elevated serum cortisol have been reported in mild heat stroke. However, hypoglycemia occurs in severe exertional heat stroke due to metabolic exhaustion. Serum potassium levels may be extremely elevated from cell lysis.

3. CNS: Direct thermal toxicity to the brain and spinal cord can rapidly produce cell death, cerebral edema, and local hemorrhage. Stupor or coma is almost universal, while seizures are common.
4. Cardiovascular: Hypotension results from high-output cardiac failure or temperature-induced myocardial hemorrhage and necrosis.
5. Renal: Acute renal failure occurs in 5% of patients with classic, and in up to 35% of cases of exertional heat stroke. Renal damage is potentiated by dehydration, cardiac failure, and rhabdomyolysis.
6. Gastroenterology: Hepatic necrosis and cholestasis occur in nearly every case (mortality 5% to 10%).
7. Hematology: Leukocytosis, anemia, and bleeding diathesis are frequently present. Disseminated intravascular coagulation is present in most cases of fatal hyperthermia and usually appears on the second or third day.
8. Pulmonary: Direct thermal injury to the pulmonary vascular endothelium may lead to cor pulmonale or the acute respiratory distress syndrome.

D. Diagnosis.

1. Heat stroke should be expected in any patient exercising in ambient temperatures >25°C or in susceptible persons during heat waves (ambient peak temperatures >32°C and minimum temperatures ≥27°C).
2. Diagnostic criteria for heat stroke include a core temperature >40°C, severely depressed mental status or coma, elevated serum creatine kinase (CK) levels, and a compatible history.
3. Profuse sweating is typical in exertional heat stroke. Lack of sweating is typical in classic heat stroke, but is *not* a requirement of diagnosis.
4. Arterial blood gas analysis should be done early in treatment, and values should be corrected for temperature due to altered solubilities of O_2 and CO_2. The net effect is that the patient is more acidotic and less hypoxemic than uncorrected values imply. For each 1°C the patient's temperature >37°C, one should increase the O_2 tension by 7.2%, increase the CO_2 tension by 4.4%, and lower the pH by 0.015.

E. Treatment.

1. Primary therapy includes immediate cooling by either evaporative or direct external methods (ice water or ice packs). A comparative study of the two methods is lacking.
2. Most cooling methods trigger cutaneous vasoconstriction and shivering. To overcome this response, simultaneous peripheral warming (while cooling the core) should be performed, using warm air or a warming blanket over the extremities.
3. External methods, such as cooling blankets, are extremely ineffective and are not recommended as the sole means of cooling.
4. Internal cooling methods (such as infusion of refrigerated 4°C saline and gastric lavages) are more rapidly effective in decreasing core temperature. Peritoneal and thoracic lavages should be considered only in extreme cases.
5. Cooling is commonly discontinued once the core temperature reaches 38°C (100.4°F), with continuation of close monitoring.

6. Dysrhythmias, metabolic acidosis, and cardiogenic failure complicate the early management of hyperthermic crisis. Hypotension should be treated initially with normal saline. Dopamine and α-adrenergic agonists should be avoided because of their tendency for peripheral vasoconstriction. Volume expansion with dextran is contraindicated due to its anticoagulant effects.
7. Osmotic therapy (mannitol 1 to 2 mg/kg or hypertonic saline) to decrease potential cerebral edema should be considered early. Due to osmotic diuresis, urine output must be followed closely and replaced with normal saline to prevent dehydration.
8. Medications: Benzodiazepines are recommended to inhibit shivering and seizures, but clinical trials are still lacking. Dantrolene is ineffective in decreasing core temperature or altering survival in heat stroke.
9. Morbidity and mortality are directly related to the peak temperature reached and the time spent at an elevated temperature. Delays in treatment of as little as 2 hours may increase the risk of death to 70%.

II. MALIGNANT HYPERTHERMIA

A. General principles.

1. Malignant hyperthermia is a drug- or stress-induced hypermetabolic syndrome characterized by vigorous muscle contractions, an abrupt increase in temperature, and cardiovascular collapse.
2. Incidence ranges between 1 of every 50,000 to 150,000 patients receiving anesthesia with a mortality between 10% and 30%.

B. Etiology.

1. Increased thermogenesis from a genetic defect of calcium metabolism in skeletal muscles causes repeated or sustained contractions after specific exposures. This reaction is not allergic in nature.
2. The metabolic predisposition to malignant hyperthermia appears to be inherited in an autosomal dominant fashion with variable penetrance and expression.
3. Halothane or succinylcholine is involved in more than 80% of cases.
4. Other agents have also been implicated: enflurane, decamethonium, gallamine, diethyl ether, ketamine, phencyclidine, and cyclopropane.
5. Stress, anoxia, viral infections, and lymphoma have been reported triggers.

C. Pathophysiology.

1. Direct thermal injury is the predominant cause of toxicity. Pathophysiologic changes mimic exertional heat stroke.
2. Vigorous muscle contractions almost immediately precipitate severe metabolic acidosis, increased CO_2 production, and elevations of CK, aldolase, and lactate dehydrogenase (due to ongoing rhabdomyolysis).
3. Hyperkalemia occurs in minutes to hours and, in combination with tissue hypoxia and acidosis, makes ventricular dysrhythmias more common.
4. Higher maximal temperatures are usually seen in malignant hyperthermia.

D. Diagnosis.

1. There is no suitable noninvasive screening test to identify susceptible persons.
2. Early signs of hyperthermic crisis vary with the agent administered but may include muscle rigidity, sinus tachycardia, mottling or cyanosis of the skin, supraventricular tachydysrhythmias, and hypertension.
3. Hyperthermia is typically a late sign in an acute crisis and is rapidly followed by hypotension, acidosis, peaked T waves on the electrocardiogram (from hyperkalemia), and malignant ventricular dysrhythmias.

E. Treatment.

1. Start dantrolene immediately to decrease thermogenesis. Concomitant use of IV dantrolene and calcium channel blockers should be avoided due to the risk of increased hyperkalemia and enhanced negative inotropy.
2. Dantrolene acts by uncoupling the excitation–contraction mechanism in skeletal muscle and by lowering intracellular myoplasmic calcium: 1 to 2.5 mg/kg of dantrolene should be given intravenously every 5 to 10 minutes, not to exceed 10 mg/kg. Oral or intravenous dosages of 1 to 2 mg/kg every 6 hours should continue for 24 to 48 hours.
3. Evaporative cooling, iced saline lavage (gastric, peritoneal), and infusion of chilled solutions may be helpful. Direct external cooling methods may be considered.
4. Ventricular fibrillation is the most common cause of early death. Procainamide increases uptake of myoplasmic calcium, and prophylactic use should be considered.
5. Prophylactic phenobarbital is strongly recommended for seizure prevention.
6. With current management techniques, mortality is <30%.

III. NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A. General principles.

1. NMS results from an imbalance of central neurotransmitters and is characterized by hyperthermia, muscular rigidity, extrapyramidal signs, and recent neuroleptic drug use.
2. Mental status changes, coma, and catatonia are common.
3. Incidence rates for NMS range from 0.07% to 2.2%.

B. Etiology.

1. The syndrome appears after receiving agents that decrease hypothalamic dopaminergic tone (typical and atypical antipsychotics) or withdrawal of dopaminergic agents.
2. Drugs acting at the D_2 dopamine-binding sites appear to have the greatest potential for causing the syndrome.

C. Pathophysiology.

1. Increased muscular rigidity, akinesia, mutism, and tremor due to hypothalamic dopaminergic imbalance.
2. Muscle rigidity generally precedes or is concurrent with hyperthermia. Peak temperatures are reached ≤48 hours of onset of symptoms.

3. Motor abnormalities vary but are typically parkinsonian extrapyramidal reactions.
4. Hyperthermia-induced comorbidity is less frequent in NMS compared to other hyperthermic syndromes because of the relatively low maximal temperatures in NMS.
5. Rhabdomyolysis and renal failure are usually mild and occur in up to 33% of patients.
6. Pulmonary complications are the most serious sequelae of NMS, including copious sialorrhea leading to aspiration pneumonia and mechanical ventilation.

D. Diagnosis.

1. Onset of symptoms typically occurs within hours of the initial dose of the triggering agent and up to 2 to 4 weeks thereafter.
2. Elevations in CK, liver function tests (lactate dehydrogenase, aspartate transaminase), and white blood cell count distinguish NMS from serotonin syndrome among patients taking neuroleptic and serotonin agonist medications simultaneously.

E. Treatment.

1. Discontinuation of the suspected offending agent.
2. Symptomatic treatment with benzodiazepines is commonly used to manage milder forms of NMS.
3. Bromocriptine (2.5 mg three times daily), amantadine (100 to 200 mg twice daily), and carbidopa/L-dopa (10 to 100 mg three times daily) increase central dopaminergic tone, thereby decreasing the central drive for muscular rigidity and thermogenesis (and directly reducing extrapyramidal side effects). Duration of treatment is usually 1 to 2 weeks.
4. Dantrolene (1 to 2.5 mg/kg IV initially followed by 1 mg/kg IV every 6 hours) may be useful in NMS cases with extreme temperature elevation and rigidity.
5. Prophylactic intubation should be strongly considered for patients with excessive sialorrhea, swallowing dysfunction, or coma.
6. Mortality rates <10% with appropriate support.

IV. DRUG-INDUCED HYPERTHERMIA

The differential diagnosis in any hyperthermic patient must include drug-induced hyperthermia caused by agents that alter central serotonin levels (e.g., serotonin syndrome). Treatment, in general, parallels that for exertional heat stroke. Death or serious morbidity due to the serotonin syndrome appears to be rare.

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55 Severe Upper Airway Infections

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I. NOSOCOMIAL SINUSITIS

A. Incidence: seen radiographically in 95% of nasotracheally intubated patients and 25% if orally intubated, although only 40% of those will have positive cultures. With strict criteria, incidence of 10% in long-term intubated patients.

B. Etiology: often polymicrobial, with gram-negative organisms are causative in two-thirds of cases. Anaerobes isolated in 0% to 15% of cases. *Staphylococcus aureus* is the most common gram-positive organism, and *Pseudomonas* species are the most common gram negative. Organism isolated from sinusitis is often identical to lower airway cultures. More unusual pathogens include:

1. Zygomycetes such as *Mucor*: associated with diabetes mellitus with ketoacidosis, burns, and renal and hepatic failure.
2. *Aspergillus* species: invasive disease in immunocompromised patients.
3. *Cryptococcus neoformans:* high mortality in immunocompromised patients.

C. Complications.

1. Orbital: orbital cellulitis and abscess, cavernous sinus thrombosis (20% mortality).
2. Intracranial: osteomyelitis, meningitis, epidural abscess, subdural empyema, and brain abscess.
3. Ventilator-associated pneumonia: causative relationship suggested by studies.
4. Fever of unknown origin (FUO): infectious sinusitis found in 53% of patients with FUO and sole cause in 16%.

D. Diagnosis.

1. Opacification on radiographs does not always indicate bacterial infection. CT scans are the imaging modality of choice. Plain films are helpful if patient unable to travel for CT.
2. Ultrasonography: 67% sensitive and 87% to 100% specific for maxillary sinusitis compared to radiographs. Improved performance when patients in semirecumbent.
3. Rhinoscopy and antral aspiration: Cultures from middle meatus do not correlate with antral lavage aspirates. High correlation between cultures obtained by antral puncture and endotracheal specimens suggests invasive sinus cultures are not usually necessary.

E. Treatment: removal of nasal tubes; decongestants; broad-spectrum antibiotics covering nosocomial gram-negative and gram-positive organisms.

With these measures, 67% of patients become afebrile in 48 hours. Surgical intervention reserved for patients who fail to respond.

F. Sphenoid sinusitis: fulminant course and high mortality if untreated. May present with severe headache, fever, and neurologic deficits (trigeminal hyperesthesia or hypoesthesia in 33% of cases). Gram-negatives organisms predominate in acute form, and mixed gram negative and positives are more common in the chronic form. Infection can extend to cavernous sinus, pituitary, and optic chiasm. Surgical drainage if symptoms persist or neurologic signs develop while on antimicrobial therapy.

II. OTOGENIC INFECTIONS

A. Mastoiditis.

1. **Pathogenesis:** Infection spreads from middle ear to mastoid air cells. Closed space infection may cause bone necrosis. Most common organisms are *S. pneumonia,* group A streptococci, *S. aureus*, and *Pseudomonas*.
2. **Presentation:** postauricular pain and fever. Half the cases follow diagnosis of otitis media. CT scans are diagnostic.
3. **Complications:** Up to 25% of patients have complications at presentation—subperiosteal abscess, meningitis, cranial nerve involvement, and sigmoid sinus thrombophlebitis.

B. Malignant otitis externa.

1. **Presentation:** most commonly in diabetic patients, with otalgia, granulation tissue in external auditory canal, and often purulent or fetid otorrhea. Infection spreads anteriorly toward parotid compartment or temporal bone. Extension leads to pain of tissues around the ear.
2. **Etiology:** *Pseudomonas aeruginosa* is the most commonly implicated pathogen.
3. **Complications:** osteomyelitis, cranial nerve paralysis, meningitis, and thrombophlebitis.
4. **Diagnosis:** CT and/or magnetic resonance imaging and technetium-99 bone scan.
5. **Therapy:** prolonged antibiotics against *P. aeruginosa* (semisynthetic penicillin or ceftazidime with an aminoglycoside). Oral fluoroquinolones have also been used. Optimal duration of treatment is unknown. Decision on surgical intervention based on response to antimicrobial treatment and the presence of complications.

III. SUPRAGLOTTITIS (EPIGLOTTITIS)

A. Presentation: infection of the structures located above the glottis, including the epiglottis, aryepiglottic folds, arytenoids, pharynx, uvula, and tongue base. The true vocal cords rarely involved. May progress to abrupt and fatal airway obstruction.

1. **Children:** usually present between ages 2 and 5 years. Course is often fulminant.
2. **Adults:** usually present at ages 40 to 60, with male preponderance. Mortality (<5%) usually due to unexpected airway obstruction.

B. Pathogenesis.

1. **Children:** inflammation mainly restricted to epiglottis because of loose mucosa on its lingual aspect. Swelling reduces the airway aperture by curling the epiglottis posteriorly and inferiorly. When edema spreads to aryepiglottic folds, inspiration draws these structures downward causing upper airway obstruction and respiratory distress.
2. **Adults:** Adult airway is relatively protected; larynx is larger and the epiglottis is shaped more like a spatula.

C. Etiology.

1. **Infectious:** *H. influenzae* type B is the most common cause in both children and adults. Declining incidence of H. *influenzae* in children since introduction of vaccine in 1995. Other bacteria, viruses, and *Candida* are also implicated.
2. **Noninfectious:** thermal injuries related to inhalation drug use, ingestion of hot food, caustic injury from aspiration, and posttransplant lymphoproliferative disorder.

D. Diagnosis.

1. **Characteristic presentation.**
   a. **Children:** starts as sore throat and/or dysphagia and progresses within hours to drooling and stridor. Four "Ds": dysphagia, dysphonia, drooling, and distress. Often prefer upright posture with neck extended and mouth slightly open.
   b. **Adults:** sore throat with or without dysphagia and frequent antecedent upper respiratory tract infections. Less common: respiratory distress, muffled voice, drooling, fever, and stridor. Hoarseness, dysphonia not observed because the process usually spares the true vocal cords.
   c. **Natural history:** Patients with an acute presentation are more likely to be infected with *H. influenzae* and have signs of upper airway obstruction, severe symptoms, fever, and leukocytosis. Without an artificial airway, the acutely ill have a higher mortality due to airway obstruction.
2. **Clinical evaluation.**
   a. **Young children:** If classic presentation, pharyngeal examination should not be attempted. Establish artificial airway in operating room. If stable, order lateral neck radiograph that may show the "thumb sign" of a swollen epiglottis.
   b. **Older children and adults:** Supraglottitis should be considered when sore throat and dysphagia are disproportionate to visible signs of pharyngitis. If no respiratory distress, examination of the larynx and supralaryngeal structures is recommended. The epiglottis may appear cherry red in color but more commonly is pale and edematous. Other supraglottic structures may be edematous, resulting in the inability to visualize the vocal cords.
3. **Diagnostic tests.**
   a. Lateral soft tissue radiograph of neck: safest when taken in the upright position. Normal radiograph does not exclude diagnosis. Direct visualization should be performed if suspicion is high.

b. Elevated white blood cell count and C-reactive protein may identify patients at higher risk.
c. Throat cultures are positive in <33%; blood cultures are rarely positive.
d. Swab culture of epiglottis by direct visualization is positive in 75%.

4. Differential diagnosis.
a. Croup: mainly viral laryngotracheobronchitis and 40 times more common than epiglottitis. Typically seen in children <3 years of age with upper respiratory tract infection of at least 48 hours.
b. Pseudomembranous croup (bacterial laryngotracheobronchitis), retropharyngeal abscess, lingual tonsillitis, and diphtheria.
c. In adults, consider infectious mononucleosis with massive tonsillar hypertrophy leading to stridor.
d. Bacterial tracheitis is a life-threatening illness with features similar to supraglottitis and viral croup. Can affect adults or children.
e. Rhinoscleroma: chronic granulomatous disorder caused by *Klebsiella rhinoscleromatis*. Nasal and oral mucous membranes are most common sites of infection, but may present acutely with upper airway obstruction due to indolent spread to the larynx and tracheobronchial tree.
f. Noninfectious causes of acute upper airway obstruction: foreign body aspiration, allergic edema, chemical laryngitis from gastroesophageal reflux, and necrotizing tracheobronchitis as a complication of mechanical ventilation. Paraquat poisoning can cause a pharyngeal membrane similar to diphtheria, accompanied by signs of shock and sepsis.

5. Treatment.
a. Airway management.
i. Early placement of artificial airway in children reduces mortality.
ii. Adults: intubation for patients with early signs of airway obstruction.
iii. Significant reductions in duration of airway control, upper airway complications, and length of hospital stay in patients with endotracheal intubation when compared to tracheostomy.
b. Antibiotics: Drug of choice is a second- or third-generation cephalosporin (cefotaxime, ceftriaxone), ampicillin/sulbactam, or trimethoprim–sulfamethoxazole if penicillin allergy. Initially give intravenously for several days, then continue by mouth for 7 to 10 days.
c. Corticosteroids: controversial in patients with infectious supraglottitis. Often used empirically, but no randomized, controlled trials. However, studies have shown that steroids are effective in children with moderate to severe croup.
d. Helium–oxygen mixture (heliox) may diminish work of breathing, providing bridge to avoid intubation.

IV. INFECTIONS OF THE DEEP SPACES OF THE NECK

A. Anatomy.

1. **Submandibular space:** also referred to as Ludwig angina.
2. **Lateral pharyngeal space (LPS):** two compartments—anterior and posterior.
3. **Retropharyngeal space (RPS):** uncommon. Usually seen in children <6 years of age.
4. **Descending infections:** Deep neck infections may extend to posterior mediastinum.

B. Etiology.

1. **Anaerobes:** *Peptostreptococcus*, *Fusobacterium* (mostly *F. nucleatum*), and *Bacteroides* (mostly *B. melaninogenicus*).
2. **Aerobic bacteria:** aerobic streptococci (mostly Streptococcus viridans) and staphylococci. Gram-negative bacilli are less common causes.

C. Submandibular space infection.

1. **Clinical presentation.**
   a. Potentially life-threatening, bacterial cellulitis of the submandibular space that can spread rapidly, by direct extension, to the submental and sublingual spaces.
   b. Odontogenic infections are implicated in up to 90% of cases.
   c. Symptoms: neck pain and swelling, tooth pain, and dysphagia. Dyspnea, tachypnea, and stridor in as many as 27%. May also present with muffled voice, drooling, and swelling of the tongue.
2. **Diagnosis:** physical examination—bilateral, firm submandibular swelling; distortion of the mouth secondary to enlargement of the tongue that is elevated and often protruding; fever; and general toxicity. Trismus (51%). Airway obstruction is frequent and life threatening.

D. Lateral pharyngeal space infections.

1. **Anterior compartment.**
   a. Presentation: unilateral trismus, systemic toxicity, induration, swelling along angle of jaw, and medial bulging of the lateral pharyngeal wall with the palatine tonsil protruding into the airway. Pain involving jaw or side of neck may be referred to ipsilateral ear and may worsen with turning the head to the unaffected side.
   b. Initial site of infection: teeth, adenoids, parotid gland, middle ear with associated mastoiditis, and lymph nodes draining the nose and pharynx.
2. **Posterior compartment:** presentation with signs of sepsis. Hypotension and respiratory alkalosis are common. Trismus and tonsillar prolapse are absent. Dyspnea is caused by edema involving the larynx and epiglottis. External swelling may be visible when infection involves parotid space, but most have no localizing signs.
3. **Complications.**
   a. Suppurative jugular venous thrombosis (most common), with bacteremia and septic emboli in one-half of cases.

b. Carotid artery involvement may lead to arteritis and false aneurysm. Carotid artery rupture, most commonly internal carotid, has 20% to 40% mortality.

c. Signs include persistent tonsillar swelling after resolution of a peritonsillar abscess, ipsilateral Horner syndrome, and cranial nerve palsies. Impending carotid rupture may be signaled by bleeding from nose, mouth, or ears; hematoma in the surrounding tissue; a protracted clinical course; or onset of shock.

4. **Diagnosis:** Contrast CT of neck provides most information. Ultrasound and MRI may be complementary. Carotid angiography may be needed to localize aneurysm before surgery.

E. RPS infections.

1. **Incidence:** uncommon but potentially fatal.
2. **Pathogenesis.**
   a. Children: Nasopharynx, pharynx, middle ear, eustachian tubes, and paranasal sinuses are the sources of most RPS abscesses.
   b. Adults: may also have history of trauma to the posterior pharynx by intubation, ingestion of foreign body, or penetrating injury.
3. **Presentation.**
   a. Children: fever and irritability; neck is often stiff and may be tilted away from the involved side. As infection progresses, may develop dyspnea and dysphagia, inability to handle secretions, respiratory distress.
   b. Adults: usually signs referable to the pharynx with fever, sore throat, dysphagia, nasal obstruction, noisy breathing, stiff neck, and dyspnea. Pain originating in or radiating to the posterior neck that increases with swallowing is most suggestive. Severe respiratory distress, particularly if accompanied by chest pain or pleurisy, suggests mediastinal extension.
4. **Diagnosis:** Lateral neck film and CT scan may detect retropharyngeal abscess.

F. Descending infections.

1. **Pathogenesis:** Deep neck infection can spread to the posterior mediastinum and diaphragms by the common pathways of the RPS and danger space (i.e., fascial plane [pathway] into the chest from the mediastinum).
   a. Descending necrotizing mediastinitis: mortality >40%. Can develop within 12 hours to as long as 2 weeks from the onset of the primary infection. Suggested by severe dyspnea, pleuritic or retrosternal chest pain during or after an oropharyngeal infection.
   b. Cervical necrotizing fasciitis: Fascial infection with muscle necrosis, often without pus or abscess formation, can progress superficially along the fascial planes of the neck and chest wall.

G. Treatment.

1. **Airway management.**
   a. Indication: if evidence of airway obstruction such as dyspnea and stridor or inability to handle secretions.
   b. Submandibular space infections: usually require tracheostomy due to upper airway obstruction. Cricothyroidotomy may be an

alternative approach, especially in emergent situations, because proximity of the tracheostomy to submandibular wounds creates risk of aspiration pneumonia and anterior mediastinitis.

c. **LPS infections:** may be complicated by trismus and intraoral swelling. Blind intubation is unsafe due to risk of trauma to the posterior pharyngeal, rupture of abscesses in the lateral pharyngeal or RPSs, and possible laryngospasm.

2. **Antimicrobial therapy.**
   a. **Drugs of choice:** penicillin with beta-lactamase inhibitor or a beta-lactamase–resistant antibiotic (cefoxitin, cefuroxime, imipenem, or meropenem) with drug highly effective against anaerobes (clindamycin or metronidazole). Add vancomycin if immunocompromised or risk for infection with methicillin-resistant *S. aureus*.
   b. **Route:** parenteral antibiotics until afebrile for at least 48 hours, then oral therapy using amoxicillin with clavulanic acid, clindamycin, ciprofloxacin, trimethoprim–sulfamethoxazole, or metronidazole.
3. **Surgery.**
   a. RPS and LPS infections usually require surgery, especially if not improving after 1 to 2 days of antibiotics.
   b. Ludwig angina often responds to antibiotics alone, but surgery required in about half of cases.

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56 Acute Infectious Pneumonia

Anna G. Rudnicki and Andres F. Sosa

I. GENERAL PRINCIPLES: Pneumonia in the immunocompetent patient.

A. Pneumonia in the intensive care unit (ICU).

1. Severe community-acquired pneumonia (CAP).
   - **a.** Criteria have been proposed by the Infectious Disease Society of America and the American Thoracic Society (Table 56-1).
   - **b.** Mortality rates for patients admitted to the ICU with CAP range from 21% to 54%.
   - **c.** Early and effective empiric therapy and ICU admission improve survival (Table 56-2).
   - **d.** Underlying comorbidity and certain medical interventions increase the risk for pneumonia and increase morbidity and mortality.
2. Nosocomial pneumonia: hospital-acquired pneumonia (HAP), occurs 48 hours after admission and was not incubating before arrival to the hospital, and ventilator-associated pneumonia (VAP), pneumonia developing after 48 to 72 hours of intubation. Health care–associated pneumonia (HCAP): Criteria include hospitalization for 2 or more days within the past 90 days, resident of nursing home or long-term acute care, receiving hemodialysis, intravenous therapy, or home wound care.
   - **a.** The infection most likely to contribute to death of hospitalized patients.
   - **b.** Risk factors for nosocomial pneumonia.
     - **i.** Underlying acute illness: predisposes to secondary pneumonia.
     - **ii.** Coexisting medical illness.
     - **iii.** Malnutrition.
     - **iv.** Other risks: general surgery, acute respiratory distress syndrome (ARDS), head injury, advanced age, obesity, cardiopulmonary disease, renal failure, malignancy, diabetes mellitus, endotracheal intubation, mechanical ventilation (VAP), tracheostomy, nasogastric tube, and use of corticosteroids, antibiotics, or H2 antagonists.
   - **c.** Additional risk factors for VAP: intubation and mechanical ventilation (risk is 3%/day first 5 days, 2%/day 5 to 10 days, and 1%/day after 10 days), reintubation, nasotracheal and nasogastric tubes, antibiotic use, colonization with virulent pathogens, aspiration (supine position), and parenteral nutrition.

TABLE 56-1 Criteria for Severe Community-Acquired Pneumonia

Major criteria
- Invasive mechanical ventilation
- Septic shock

Minor criteria
- Respiratory rate ≥ 30 breaths/min
- $Pao_2/Fio_2 \leq 250$
- Multilobar infiltrates
- Mental status changes
- Uremia
- Leukopenia (WBC <4,000 cells/mm^3)
- Hypothermia (core temp, <36°C)
- Hypotension
- Elevated lactate, hypoglycemia, hyponatremia, metabolic acidosis
- Cirrhosis
- Asplenia

ICU admission is recommended for any major or three minor criteria.
BUN, blood urea nitrogen; Pao_2/Fio_2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.
Source: Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults.

II. PATHOGENESIS: Understanding normal host defenses (e.g., humoral immunity, cough) and their potential impairments is valuable in assessing those at risk for pneumonia in general and select pathogens in specific (e.g., *Pneumocystis jiroveci* with impaired cellular immunity). A more thorough discussion of this topic is referenced.

III. ETIOLOGY

A. Severe CAP.

1. Organism causing pneumonia identified in approximately 50%.
2. Most common organisms leading to ICU admission for CAP: pneumococcus, *Legionella pneumophila,* epidemic viruses (influenza), *Staphylococcus aureus* (including MRSA), and enteric gram-negative bacilli.
3. In specific clinical settings, certain pathogens may be more common (e.g., injection drug use, *S. aureus;* neutropenia, *Pseudomonas aeruginosa).*

B. Nosocomial pneumonia.

1. Early-onset HAP occurs within the first 4 days of hospitalization; likely pathogens are similar to CAP.
2. Late-onset HAP occurs 5 days or more from hospital admission, HCAP, and VAP caused by a variety of gram-positive and gram-negative bacteria, many of which are multidrug resistant (MDR).
3. More common organisms: gram-negative bacilli such as *P. aeruginosa, Escherichia coli, Klebsiella pneumoniae, and Acinetobacter.*

TABLE 56-2 Empiric Therapy for Nosocomial Pneumonia Requiring ICU Admission

Pneumonia type	Potential pathogens	Recommended antibiotic for patient type
Early-onset HAP, no RFs for MDRs	Core organisms[a]	beta-lactam **plus** macrolide or a respiratory fluoroquinolone
Late-onset HAP, VAP, and HCAP or with risk factors for MDR pathogens	Core organisms[a] Plus MDR pathogens[b] Plus consider[c] *L. pneumophila.* and MRSA	Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or beta-lactam/beta-lactamase inhibitor (piperacillin–tazobactam) Plus Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) Or Aminoglycoside (amikacin/gentamicin/tobramycin) Plus Linezolid or vancomycin

[a]Core organisms: *S. pneumoniae, H. influenzae*, methicillin-sensitive *S. aureus*, and nonresistant gram-negative bacilli.
[b]MDR pathogens: *P. aeruginosa*, *K. pneumoniae*, and *Acinetobacter* spp.
[c]If an environmental source of *Legionella* is present, with a known nosocomial outbreak, use fluoroquinolone in the regimen.

4. Also see gram positives: *S. aureus, coagulase-negative Staphylococcus, and Enterococci.*
5. *P. aeruginosa:* more common, especially with steroid use, structural lung disease, and neutropenia.

IV. CLINICAL PRESENTATION

A. CAP.

1. Signs and symptoms depend on host and bacterial factors. Patients with altered immune function have a more subtle clinical presentation.
2. Classic symptoms: fever, chills, dyspnea, pleuritic chest pain, productive cough. Elderly patients may have more indolent presentation (confusion, altered functional capacity).

B. Nosocomial pneumonia.

1. Clinical diagnosis is poor.
2. Most clinical definitions of nosocomial pneumonia require purulent sputum, leukocytosis, fever, and a new and persistent infiltrate in a hospitalized patient.

V. DIAGNOSIS

A. History.

1. Pneumonia should be classified as to environmental site of origin and thus classified as CAP, HCAP, early-onset HAP, and late-onset HAP (including VAP).
2. In addition to usual symptoms, consider comorbid illness, medication use including recent antibiotics, history of immunosuppression, recent diagnosis/history of influenza, geographic and travel history, and exposure to animals. This information does not help in diagnosis but broadens the list of initial diagnostic possibilities with respect to specific pathogens.

B. Physical examination: not specific for diagnosis of pneumonia. Findings may help predict severity of disease. Consider presence of pleural effusion.

C. Diagnostic testing.

1. Routine laboratory tests: complete blood count, routine chemistry studies, and blood cultures; assess oxygenation.
2. Chest radiography: may suggest a specific pathogen but not diagnostic. Multilobar involvement carries worse prognosis. Look for pleural effusion and cavitation as well.
   a. Limitation of chest radiograph (CXR) in the ICU must be recognized. Consider noninfectious pneumonia mimics.
3. Sputum examination: Consider sputum culture for patients with CAP requiring ICU admission. Sputum or lower respiratory tract culture recommended for nosocomial pneumonia. Also consider sputum evaluation for atypical, opportunistic, or resistant organisms or tuberculosis in proper setting.
4. Culture: definitive diagnosis only if cultures of blood, pleural, lung, or spinal fluid are positive.
   a. Bacteremia is uncommon: 15% or less with CAP and 8% to 15% with nosocomial pneumonia.
   b. Expectorated sputum: difficult to interpret (infection vs. colonization).
5. Serology: routine testing not recommended. Standard for diagnosis of atypical bacteria (*Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Legionella* other than pneumophila). Empiric antibiotic therapy will be completed before the earliest time point to check convalescent-phase serum.
6. Antigen testing: routine urinary *Legionella* antigen (yield of 70% to 90% for serogroup-1, which comprises 80% to 95% of cases) and urinary pneumococcal antigen are recommended by Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines in pneumonia requiring the ICU.
7. Invasive diagnostic culture.
   a. Flexible bronchoscopy.
      i. Bronchoscopy for diagnosis of VAP is controversial. In intubated and ventilated patients, similar clinical outcomes occur with endotracheal cultures and protected specimen brush (PSB) cultures.

ii. Bronchoalveolar lavage (BAL): valuable in establishing nonbacterial causes of infection, especially in the immunocompromised patient.

b. Open lung biopsy: gold standard for the diagnosis of infection; most often used in the immunocompromised host to rule out noninfectious disease.

D. Differential diagnosis: In the critically ill, diseases that mimic pneumonia such as congestive heart failure, pulmonary embolism, and malignancy may be more common.

VI. TREATMENT

A. Supportive therapy.

1. Nutritional therapy: evaluation and support early in the course.
   a. Enteral nutrition preferred; data suggest better preservation of immune function.
   b. Gastric (vs. postpyloric) feeding tubes with continuous feeds are equivalent with respect to aspiration. Exception may be in those with gastric ileus.
2. Chest physical therapy (CPT): CPT reserved for patients with high volume of sputum and ineffective cough. Also to treat lobar atelectasis.
3. Aerosols humidity: have little impact. May provoke cough. Mucolytics (e.g., *N-acetylcysteine)* can precipitate bronchospasm. β2-Adrenergic bronchodilators may enhance mucociliary clearance, though are best reserved for patients with chronic obstructive pulmonary disease or asthma.

B. Antibiotic therapy: Early (within 4 hours of arrival) and effective antibiotic therapy improves survival in severe CAP.

1. Severe CAP.
   a. Initial therapy: third-generation cephalosporin, plus a macrolide, given intravenously. Alternative is fluoroquinolone plus third-generation cephalosporin.
   b. When *P. aeruginosa* considered: antipseudomonal beta-lactam and antipseudomonal quinolone or aminoglycoside.
   c. Fluoroquinolone monotherapy should not be used for severe CAP.
   d. Also consider covering for community-acquired MRSA with vancomycin.
2. Nosocomial pneumonia.
   a. Treat common pathogens; consider local patterns of infection, resistance, and antibiotic use. Broad initial coverage, narrowed on culture result, most effective.
   b. For patients with early-onset (first 4 days of hospitalization) HAP, no antibiotics in last month, and no risk factors for HCAP, then can treat with antibiotics for CAP (see Table 56-3).
   c. With risk for *Pseudomonas* or highly resistant gram-negative bacillary pathogen (i.e., *Acinetobacter*, *Enterobacter*, *Klebsiella*, *Stenotrophomonas*), use combination therapy until cultures demonstrate the absence of such organism.

TABLE 56-3 Risk Factors for Multidrug-Resistant Pathogens

Antimicrobial therapy in preceding 90 d
Current hospitalization of 5 d or more
High frequency of antibiotic resistance in the community or hospital
Presence of multiple risk factors for HCAP
Hospitalization for 2 or more days in preceding 90 d
Residence in nursing home or extended care facility
Home infusion therapy
Chronic dialysis within 30 d
Home wound care
Family member with multidrug-resistant pathogen
Immunosuppressive disease or therapy

d. Treatment of VAP for 8 days showed same outcome as 15 days (nonlactose fermenting gram negatives had lower relapse rates with 15-day regimen).

e. Linezolid is equally effective as vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) VAP.

f. De-escalation strategy is recommended. Reassess cultures, clinical response, and antibiotics every 3 days. Adjust antibiotics as indicated. If low suspicion and negative cultures, stop antibiotics after 3 days.

3. Antibiotic resistance.

a. The frequency of resistance among community-acquired organisms and nosocomial pathogens is increasing. An understanding of local resistance patterns is required. See Table 56-3 for risk factors for multidrug-resistant pathogens.

b. Prevention of VAP: Evidence-based strategies include orotracheal intubation; orogastric tubes instead of nasogastric; changes of ventilator circuits only for new patient and if circuits soiled; use of closed endotracheal suction systems; an effective hand hygiene program; frequent oropharyngeal care; and semirecumbent positioning no lower than 30 degrees. Also consider aspiration of subglottic secretions, silver-coated endotracheal tubes, kinetic beds, restricted blood transfusion, and postpyloric feeding (with significant gastric ileus); avoid reintubation.

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SECTION 5

Renal Problems in the Intensive Care Unit

Pang-Yen Fan

57 Metabolic Acidosis and Metabolic Alkalosis

Jahan Montague and Jason Kurland

I. METABOLIC ACIDOSIS

A. General principles.

1. **Background information.**
   - **a.** The pH of extracellular fluid, normally between 7.36 and 7.44, is tightly regulated, largely by the bicarbonate buffer system. Preservation of this buffer system depends on
     - **i.** Reclamation of filtered bicarbonate, principally in the proximal tubule.
     - **ii.** Elimination of 50 to 100 mEq of metabolically generated hydrogen ion each day. These hydrogen ions are actively secreted by the nephron and buffered in the urine either by filtered buffers, such as phosphate anion, or by ammonia.
2. **Definition.**
   - **a.** A metabolic acidosis is characterized by a low arterial pH and reduced plasma bicarbonate. However, the actual pH and bicarbonate depend on the balance of all acid–base abnormalities.
3. **Classification.**
   - **i.** Metabolic acidosis is classified as either normal or expanded anion gap (AG). The normal AG is between 6 and 12 mmol/L.

TABLE 57-1 Etiology of Metabolic Acidosis with a Normal AG

Pathogenesis	Etiology	Mechanism
Bicarbonate loss	Type 2 renal tubular acidosis	Inadequate proximal tubular bicarbonate reabsorption
	Diarrhea	Bicarbonate loss from gut
	Ileostomy	
	Laxative abuse	
	Pancreatic fistula	
	Biliary drain	
	Bladder-drained pancreas transplant	
	Intestinal neobladder	
H ion retention	Type 1 renal tubular acidosis	Failure of distal nephronal proton pumps
	Type 4 renal tubular acidosis (hypoaldosteronism)	Impaired ammonia production
Hydrogen chloride overload	Parenteral alimentation	Exogenous hydrogen ion

ii. The AG (representing unmeasured anions) is calculated by the following equation:

$$AG = Na^+ - \left[Cl^- + HCO_3^-\right]$$

B. Etiology.

1. Acidosis with a normal AG (hyperchloremic acidosis). See Table 57-1.
2. Acidosis with an expanded AG (high AG). See Table 57-2.

C. Pathogenesis.

1. Acidosis with a normal AG.
   - **a.** Decrement in plasma bicarbonate concentration is matched by an increase in chloride.
   - **b.** See Table 57-1 for etiologies and mechanisms.

TABLE 57-2 Etiology of Metabolic Acidosis with a High AG

Metabolic acidosis with a high AG

Lactic acidosis: lactate, D-lactate
Ketoacids: diabetic, alcoholic, and starvation ketoacidosis
Renal failure: A heterogenous group of organic anions accumulate in uremia.
Ingestions/toxins
- Methanol
- Ethylene glycol
- Propylene glycol
- Salicylates

2. Acidosis with an expanded AG.
   a. Accumulation of organic acid reduces plasma bicarbonate concentration. For example, lactic acid is composed of a hydrogen cation and lactate anion. In lactic acidosis, excess hydrogen ions are buffered and each bicarbonate molecule consumed is then replaced by a lactate molecule. Since lactate is an unmeasured anion, its retention results in an apparent increase in the AG.

D. Diagnosis.

1. **Clinical presentation.**
   a. Physical examination often reveals Kussmaul respirations (deep, rapid), reflecting respiratory compensation.
2. **Laboratory studies.**
   a. Diagnosis of metabolic acidosis.
      i. An uncomplicated metabolic acidosis is characterized by a low blood pH in association with a reduced plasma bicarbonate concentration. Note: When multiple acid–base abnormalities are present, pH and/or bicarbonate concentration may be normal despite the presence of an acidosis (see below).
   b. Hyperkalemia.
      i. Hyperkalemia may result from egress of potassium from cells as hydrogen ions enter.
3. **Respiratory compensation.**
   a. Respiratory compensation for metabolic acidosis is caused by chemical stimulation of the brainstem respiratory centers.
   b. To assess respiratory compensation, the following formula may be used:

$$\text{Expected } Pco_2(\text{mm Hg}) = [(1.5 \times Hco_3) + 8] \pm 2$$

4. **Multiple acid–base disturbances.**
   a. Calculation of the Δ/Δ ratio (the ratio of AG increase to bicarbonate decrease) is used to screen for multiple acid–base disturbances:

$$\Delta / \Delta \text{ratio} = \Delta \text{anion gap} / \Delta Hco_3$$

$$= \left(\text{Measured anion gap} - \text{normal anion gap}\right) / \left(\text{Normal } Hco_3 - \text{measured } Hco_3\right)$$

      i. Metabolic alkalosis and metabolic acidosis can occur simultaneously. For example, a patient with diabetic ketoacidosis (DKA) may also have vomiting (metabolic alkalosis). These two acid–base disturbances offset each other so that the pH and bicarbonate concentration may be normal. The acidosis can be detected by the elevated AG. The alkalosis can be detected by a normal bicarbonate concentration despite an elevated AG. In contrast, with a simple AG metabolic acidosis, the bicarbonate level should drop commensurately with the increase with the AG. Note that the Δ/Δ ratio is usually >1.0, even in simple metabolic acidosis. A ratio >1.6 suggests concomitant metabolic alkalosis.

ii. Multiple superimposed metabolic acidoses: For example, a patient with diarrhea develops DKA. The simultaneous hyperchloremic normal AG acidosis (from the diarrhea) and expanded AG acidosis (from the ketoacidosis) result in a drop in bicarbonate far exceeding the increase in the AG. The Δ/Δ ratio <1 suggests concomitant normal and expanded AG metabolic acidoses.

5. **Treatment.**
   a. Invariably, the best approach to therapy of metabolic acidosis is to treat its underlying cause rather than giving bicarbonate.
   b. Bicarbonate supplementation can be used in individuals with non-anion metabolic acidosis. In patients with a high anion-gap acidosis, bicarbonate supplementation can be considered in patients with a systemic pH below 7.15 and serum bicarbonate below 10, but there are little data to support this approach.
   c. The therapeutic goal is to raise the pH to approximately 7.20. Rapid normalization of pH with bicarbonate therapy should be avoided.
   d. Bicarbonate is typically given in an isotonic solution such as 5% dextrose in water (D5W) with 150 mEq/L sodium bicarbonate.
   e. Specific approaches to the therapy of DKA, lactic acidosis, the acidoses associated with toxic ingestions, and the acidosis of renal failure are found elsewhere in this book (see Chapters 83 and 96).

II. METABOLIC ALKALOSIS

A. General principles.

1. **Definition.**
   a. The findings of an elevated plasma pH and bicarbonate concentration establish the diagnosis of metabolic alkalosis.
2. **Classification.**
   a. Metabolic alkalosis is classified into two categories: chloride-responsive and chloride-resistant alkalosis (see Table 57-3).

B. Etiology.

1. See Table 57-3.

C. Pathogenesis.

1. Generative phase: Metabolic alkalosis can be generated in three ways.
   a. Loss of hydrogen ion.
      i. Vomiting and nasogastric suction result in the loss of gastric secretions rich in hydrogen and chloride ions.
      ii. Mineralocorticoid excess states, such as hyperaldosteronism, Cushing syndrome, and Liddle syndrome, are characterized by enhanced distal tubular sodium reabsorption and hydrogen ion secretion.
   b. Exogenous bicarbonate loading.
   c. Loss of fluid with a higher chloride-to-bicarbonate ratio than that of normal extracellular fluid (contraction alkalosis). This can be seen with both loop and thiazide diuretics.

TABLE 57-3 Etiologies of Metabolic Alkalosis

Chloride-responsive alkalosis (urine chloride <15 mEq/L)	Chloride-resistant alkalosis (urine chloride >20 mEq/L)
Vomiting	Mineralocorticoid excess
Nasogastric suction	Exogenous alkali loading
Recent diuretic use	Ongoing diuretic use
Posthypercapnia	Severe hypokalemia
Exogenous alkali loading[a]	Bartter syndrome and related disorders

[a]Urine chloride level indicates if metabolic alkalosis is related to hypovolemia (low urine chloride) or other factors such as mineralocorticoid excess or intrinsic renal tubular damage (high urine chloride).

2. Maintenance phase: Excess bicarbonate is normally rapidly excreted. This process is impaired if hypovolemia, chloride depletion, and hypokalemia are present. These abnormalities result in enhanced renal bicarbonate absorption and increased H excretion, which perpetuates the metabolic alkalosis.

D. Diagnosis.

1. Clinical presentation.

a. Alkalemia itself is relatively free of adverse clinical effects. Most of the symptoms, such as muscle spasm, paresthesias, and weakness, are more directly attributable to associated electrolyte imbalances, such as hypokalemia and reduced ionized calcium, as well as hypovolemia.

b. Patients should be questioned for vomiting and diuretic use. Bulimic patients and persons who abuse diuretics may not yield this information willingly.

c. The presence of hypertension in a patient with hypokalemic alkalosis should raise suspicion of a mineralocorticoid excess state such as primary hyperaldosteronism or Cushing disease.

d. Physical examination should include volume assessment, blood pressure, careful assessment of body habitus, and evidence for vomiting (loss of tooth enamel, parotid gland enlargement, and excoriations of the fingers).

2. Laboratory studies.

a. Metabolic acidosis is characterized by the presence of both an elevated serum bicarbonate concentration and plasma pH.

b. When metabolic alkalosis coexists with metabolic acidosis, the bicarbonate level may be normal.

c. Urine chloride of <15 mEq/L is typical of chloride-responsive alkalosis and >20 mEq/L of chloride-resistant alkalosis (Table 57-3).

E. Treatment.

1. Principles.

a. Emergency treatment of metabolic alkalosis is rarely necessary because of the relative paucity of adverse effects associated with this

disorder. When blood pH is extremely high >7.55, urgent therapy should be contemplated.

b. Chloride-responsive alkalosis.

i. Chloride-responsive alkalosis is typically associated with volume depletion. Volume repletion with normal saline is usually effective.

ii. Hypokalemia should be repleted aggressively.

iii. For patients with persistent vomiting or those receiving continuous nasogastric suctioning, H_2 blockers or proton pump inhibitors can be used to reduce gastric acid output.

iv. Acetazolamide (250 mg intravenously or orally one to four times daily) may be given to enhance renal bicarbonate excretion.

v. In rare cases of severe metabolic alkalosis resistant to conventional therapies, 0.1 N hydrochloric acid can be used.

c. Chloride-resistant alkalosis: Therapy of chloride-resistant metabolic alkalosis should be directed at the underlying cause. Associated electrolyte abnormalities such as hypokalemia should be corrected.

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58 Disorders of Plasma Sodium and Potassium

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I. DISORDERS OF PLASMA SODIUM

A. General principles.

1. Plasma sodium (PNa) is the major determinant of plasma osmolality (Posm), which can be estimated as follows:

$$\text{Posm} = 2 \times (\text{Na mEq / L}) + (\text{glucose mg / dL}) / 18 + (\text{BUN mg / dL}) / 2.8$$

2. PNa disorders generally indicate abnormal water metabolism, rather than abnormal sodium metabolism.

3. Posm is tightly regulated by antidiuretic hormone (ADH).

4. Increased ADH leads to water absorption via urinary concentration (high Uosm).

5. Decreased ADH leads to water excretion through urinary dilution (low Uosm).

B. Hyponatremia.

1. Etiology: Tables 58-1 and 58-2.

2. Pathophysiology.

a. Hypovolemia.

i. Kidney retains Na and water in response to hypoperfusion from volume depletion.

ii. Urinary indices reflect both sodium avidity with low urine Na and low fractional excretion of Na (FENa) and water avidity (high Uosm).

iii. Sodium deficit exceeds water deficit.

b. Hypervolemia.

i. Kidney retains Na and water in response to hypoperfusion despite volume expansion (ineffective circulating volume).

ii. Urinary indices reflect both sodium avidity (low urine Na and low FENa) and water avidity (high Uosm).

iii. Water excess exceeds sodium excess.

c. Euvolemia.

i. With syndrome of inappropriate antidiuretic hormone secretion (SIADH), kidney retains water inappropriately, but handles Na normally.

ii. Urinary indices typically reflect water avidity (high Uosm), but urine Na and FENa are not low.

TABLE 58-1 Causes of Hyponatremia

Hypovolemic
- GI fluid losses (vomiting, diarrhea, enterostomy output, nasogastric drainage)
- Renal fluid losses (diuretics, hyperglycemia-induced osmotic diuresis)
- Transdermal fluid losses (excessive sweating, fever)
- Cerebral salt wasting (CNS trauma or tumor; urine sodium >40 mEq/L)

Hypervolemic
- Ineffective circulating volume (cardiomyopathy, cirrhosis, nephrotic syndrome, third spacing)

Euvolemic
- SIADH
- Reset osmostat
- Endocrine disorders (adrenal insufficiency, hypothyroidism)
- Psychogenic polydipsia
- Reduced solute intake
- Renal failure

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

iii. With reset osmostat, water metabolism occurs normally, but maintains an abnormally low PNa.

iv. With psychogenic polydipsia and inadequate solute intake, water intake exceeds renal water excretory capacity and Uosm will be low.

v. With renal failure, water excretion is limited by low urine output.

3. Diagnosis.

a. Clinical presentation.

i. Symptoms principally neurologic, but rarely focal.

ii. Range from no symptoms to fatigue, lethargy, gait disturbances, confusion, nausea, vomiting, or, in severe cases, seizures and coma.

iii. Severity of symptoms relates to both level of hyponatremia and the rapidity of its development.

TABLE 58-2 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

Pulmonary disease
Central nervous system disease
Ectopic ADH production (carcinoma, especially small cell lung)
Medications (cyclophosphamide, carbamazepine, chlorpropamide, NSAIDs, cisplatin, SSRI, ecstasy [MDMA], etc.)
Exogenous ADH or oxytocin
HIV infection (from central nervous system, pulmonary, and malignant causes)
Pain (often postoperative)
Idiopathic

NSAIDs, nonsteroidal anti-inflammatory drugs; HIV, human immunodeficiency virus; SSRI, selective serotonin reuptake inhibitor.

b. History and physical examination.
  i. Assessment of volume and neurologic status.
  ii. Estimation of acuity of hyponatremia.
  iii. Review of medications.
  iv. Evaluation of solute and water intake and losses.
c. Laboratory studies.
  i. Measured Posm: Normal value with a low calculated Posm indicates pseudohyponatremia (hyperlipidemia, hyperproteinemia).
  ii. Uosm: Maximally dilute urine with Uosm (50 to 100 mOsm/kg) suggests primary polydipsia.
  iii. Urine sodium.
    (a) Typically <20 mEq/L with volume depletion or ineffective circulating volume.
    (b) >20 mEq/L with SIADH.
  iv. For euvolemic hyponatremia, assess renal, adrenal, and thyroid function, and obtain chest radiograph (CXR) and head computed tomography (CT).
  v. Uric acid: Levels <4 mg/dL suggest SIADH.

4. Treatment.
a. Rate of correction over the first 24 to 48 hours may be more important than rate over a single or first few hours.
  i. Avoid rapid correction due to risk of osmotic demyelination.
b. Asymptomatic patients: increase PNa < 0.5 mEq/hour and <8 mEq/24 hours.
  i. If mildly symptomatic, increase Na up to 1.0 mEq/L/h for 3 to 4 hours then slow the rate of correction to raise PNa ≤ −10 mEq/L over the initial 24 hours.
  ii. If severely symptomatic (seizures, coma), increase PNa 1 mEq/L/h × 4 to 6 hours then slow rate of correction to total of 8 to 10 mEq/L over 24 hours.
c. Monitor PNa every 2 hours for rapid correction.
d. Do not correct to normal PNa; target PNa should be 120 to 130 mEq/L.
e. Rapid correction requires hypertonic saline (512 Na mEq/L) infusion.
f. Calculate Na deficit (amount of Na to raise PNa to target).

$$\text{Weight} \times 0.6(\text{target PNa} - \text{current PNa}) = \text{Na deficit}$$

$$\text{Volume(mL) of hypertonic saline needed to correct Na deficit} = (\text{Na deficit}/512) \times 1{,}000$$

$$\text{Infusion rate (L / hour)} = \text{volume of hypertonic saline needed} / (\text{target PNa} - \text{current PNa}) / \text{desired correction rate}$$

g. Hypovolemia.
  i. Isotonic saline to correct volume deficit.
  ii. In the setting of hypovolemia, each liter of saline will increase PNa ~1 mEq/L.
  iii. Correction of hypovolemia will suppress ADH and subsequently lead to rapid water excretion.

h. Hypervolemia.
  i. Water restriction.
  ii. Loop diuretics (avoid thiazides, which may exacerbate hyponatremia).
  iii. Vasopressin antagonists.
    (a) Only indicated in euvolemic/hypervolemic hyponatremia.
    (b) NOT indicated for hyponatremic emergencies.
    (c) Expert consultation recommended for initiation of therapy.
i. Euvolemic.
  i. Water restriction.
  ii. Hypertonic saline.
  iii. Vasopressin antagonists.
  iv. Correction/treatment of precipitating disorder.

C. Hypernatremia.

1. Etiology: See Table 58-3.
2. Pathophysiology.
  a. Defect in ADH production, release, or effect with subsequent renal water losses.
  b. Inadequate replacement of water losses.
  c. Sodium overload.
3. Diagnosis.
  a. Clinical presentation.
    i. Symptoms principally neurologic, but rarely focal.
    ii. Range from no symptoms (chronic hypernatremia) to thirst, lethargy, weakness, and irritability; with severe cases, neuromuscular irritability, seizures, and coma.
    iii. Brain volume loss from acute hypernatremia can also cause structural tearing of small blood vessels and venous sinus thrombosis.
  b. History and physical examination.
    i. Assessment of volume and neurologic status.

TABLE 58-3 Causes of Hypernatremia

Water loss
GI losses
Renal losses
Diuretics
Hyperglycemia-induced osmotic diuresis
Central or nephrogenic diabetes insipidus
Insensible and transdermal losses (excessive sweating, fever, burns)
Inadequate intake
Limited access to water
Primary hypodipsia
Hypothalamic lesions affecting osmoreceptor function
Sodium overload
IV sodium bicarbonate administration
Hypertonic saline
Salt tablets

ii. Estimation of acuity of hypernatremia.
iii. Review of medications.
iv. Evaluation of solute and water intake and losses (especially urine output).
v. Evaluation of thirst.

c. Studies.
i. Uosm.
(a) Near maximal (800 mosmol/kg) suggests inadequate water intake or sodium overload.
(b) Low Uosm suggests either central (ADH-deficient) or nephrogenic (ADH-resistant) diabetes insipidus. Near isotonic Uosm may suggest osmotic diuresis.
ii. Urine sodium: Low (<20 mEq/L) suggests concomitant volume depletion.
iii. ADH challenge.
(a) In setting of Posm >295, high urine output, and low Uosm, consider test dose of 1-deamino-8-D-arginine vasopressin (DDAVP) (4 μg subcutaneously).
(b) Immediate significant decrease in urine output and increase in Uosm suggest central diabetes insipidus.
(c) Lack of response suggests nephrogenic diabetes insipidus.
(d) Results may be inconclusive due to incomplete defects in ADH level or response.
(e) ADH level may then be helpful.
iv. Water deprivation test.
(a) Useful to assess etiology of hypernatremia in patient whose PNa has already been corrected to normal.

4. Treatment.
a. Estimate water deficit.

$$(\text{Weight} \times 0.5)\ (\text{PNa} / 140 - 1) = \text{Water deficit in liters.}$$

b. Replete deficit with D5W infusion or enteral water boluses.
c. Rate of replacement = water deficit/desired rate of correction.
d. Use a rate of correction based on signs and symptoms.
i. Symptomatic patients should be corrected rapidly (up to 2 mEq/L/h), but <12 mEq/L in 24 hours.
ii. Asymptomatic patients should be corrected slowly (up to 0.5 mEq/hour) but <10 mEq/L in 24 hours.
iii. For hypovolemic patients, correct volume deficit first with saline before correcting water deficit.
iv. For hypervolemic patients, diurese in addition to correcting water deficit.
e. Increase water replacement rate accordingly to replace ongoing water losses as well as prior deficit.
f. If possible, correct the underlying disorder or remove the offending drug.
i. For central diabetes insipidus, DDAVP by nasal spray (5 to 20 μg once or twice a day).

ii. For nephrogenic diabetes insipidus, thiazide diuretics diminish polyuria by inducing mild volume depletion and enhancing proximal tubular reabsorption of water.
iii. Some patients with incomplete nephrogenic diabetes insipidus may respond to supraphysiologic doses of DDAVP.

5. Complications.
   a. With overly rapid correction, cerebral edema may develop.

II. PLASMA POTASSIUM DISORDERS

A. General principles.

1. 98% of potassium (K) is intracellular.
2. Plasma potassium levels principally reflect shifts between extra- and intracellular compartments and correlate poorly with total body potassium.
3. Transcellular K shifts are mediated by insulin, β_2-adrenergic stimulation, Posm, and pH.
   a. Insulin and β_2-adrenergic stimulation shift K intracellularly.
   b. High Posm shifts K extracellularly (solute drag).
   c. Acidosis can shift K extracellularly and alkalosis shifts K intracellularly.

B. Hypokalemia.

1. Etiologies: See Table 58-4.
2. Diagnosis.
   a. Clinical presentation: muscle weakness, cramps, rhabdomyolysis, paresthesias, ileus, orthostatic hypotension, polyuria, and arrhythmias.
   b. History and physical examination.
      i. Evaluate dietary intake (consider anorexia).
      ii. Assess volume status.
      iii. Review medications (consider laxative and diuretic abuse).
      iv. Assess gastrointestinal (GI) losses (consider bulimia).
   c. Studies.
      i. Electrocardiogram (ECG): T wave depression, prominent U waves, and arrhythmias.
      ii. Urinary potassium: If <25 to 30 mEq/day, kidney is appropriately conserving K, and any ongoing K losses are likely from GI tract.
      iii. Magnesium (Mg) level (adequate Mg necessary for correction of low K).
3. Treatment.
   a. Plasma levels from 3 to 3.5 mEq/L.
      i. Generally does not produce symptoms.
      ii. May cause arrhythmias in patients with heart disease (especially if taking digitalis).
   b. Monitor K closely to avoid "overshoot" hyperkalemia, especially in setting of poor renal function.
   c. Consider cardiac monitoring, especially for patients with cardiac disease.

TABLE 58-4 Causes of Hypokalemia

Decreased intake
K loss
GI losses
Vomiting
Diarrhea
NGT drainage
Renal losses
Diuretics
Polyuria (hyperglycemia-induced osmotic diuresis, polydipsia)
Mineralocorticoid excess
Severe metabolic alkalosis
Renal tubular acidosis
Hypomagnesemia
Amphotericin B
Salt-wasting nephropathies (e.g., Bartter syndrome, tubulointerstitial disease, hypercalcemia)
Nonreabsorbable anions (e.g., penicillin derivatives from high-dose therapy)
Transdermal losses
Dialysis
Increased entry into cells
Increased extracellular pH
Increased availability of insulin
Elevated β_2-adrenergic activity (e.g., high catecholamine states)
Hypokalemic periodic paralysis
Marked increase in blood cell production
Hypothermia

NGT, nasogastric tube.

d. Correct any concomitant Mg deficiency.

e. For severe hypokalemia, delay (if possible) correction of concomitant metabolic acidosis as increase in pH could aggravate hypokalemia by shifting K intracellularly.

f. If diuretic-induced hypokalemia, consider adding or converting to potassium-sparing diuretic.

g. For parenteral K repletion, avoid intravenous (IV) fluids with dextrose, which stimulate insulin release and shift K intracellularly.

h. In diabetic ketoacidosis, begin K repletion early ($K \leq 4.5$ mEq/L) as treatment will "unmask" a larger underlying K deficit than is initially evident.

4. Dosing guidelines.

a. 40 mEq KCl can transiently raise plasma K up to 1 mEq/L, but K will decrease quickly after equilibration.

b. Give adequate repletion as plasma K of 2 mEq/L may reflect a total K deficit of 400 to 800 mEq.

c. Rates of IV K repletion >10 to 20 mEq/L/hour require central access and should be used only in extreme circumstances due to the risk of cardiac arrhythmias.

C. Hyperkalemia.

1. Etiologies: See Table 58-5.

2. Diagnosis.

a. Clinical presentation.

i. Abnormal skeletal and cardiac muscle function including weakness, paralysis, and arrhythmias.

ii. Severe symptoms may occur with levels above 7.5 mEq/L, but substantial interpatient variability exists.

b. History and physical examination.

i. Dietary assessment.

ii. Review of medications.

iii. Evaluate muscle strength.

c. Studies.

i. ECG: symmetric T wave peaking, reduced P wave voltage, widening of QRS complexes, and ultimately a sinusoidal pattern.

ii. ECG may not show changes despite higher levels, especially if the rate of K rise has been slow.

TABLE 58-5 Causes of Hyperkalemia

Increased K intake
TPN
K-rich diet
K-based salt substitutes
Transcellular K shift
Pseudohyperkalemia
Metabolic acidosis
Insulin deficiency
Hyperosmolality (hyperglycemia)
Tissue catabolism and necrosis
Hemolysis
β-Adrenergic blockade
Exercise
Digitalis overdose
Hyperkalemic periodic paralysis
Trimethoprim
Reduced urinary potassium excretion
Hypoaldosteronism
Type 4 renal tubular acidosis (RTA)
Medications
ACEIs, ARBs, NSAIDs, trimethoprim, heparin, aldosterone antagonists
Renal failure
Renal tubular disorders
Adrenal insufficiency
Severe renal hypoperfusion
Urinary tract obstruction

TPN, total parenteral nutrition; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

3. Treatment.
   a. K < 6.5 mEq/L without ECG changes.
      i. Dietary K restriction to <2 g/day.
      ii. Discontinue precipitating medications.
      iii. Increase K elimination through diuretics or oral cation exchange resins.
   b. Severe or symptomatic hyperkalemia (>6.5 mEq/L, or lower level with ECG changes).
   c. Implement treatment to rapidly lower plasma K or reduce electrophysiologic effects.
      i. Calcium (10 mL of 10% calcium gluconate IV) stabilizes cell membranes rapidly but only for 15 to 30 minutes. Use for significant ECG changes (widened QRS complex or loss of P waves). Can induce digitalis toxicity.
      ii. IV insulin (10 units of regular) and glucose (50 mL of D50) induce intracellular K shift and can decrease K by 0.5 to 1.5 mEq/L. Act in 15 to 30 minutes and last for several hours.
      iii. Sodium bicarbonate: 50 mEq IV induces intracellular K shift in patients with metabolic acidosis. Acts within 30 to 60 minutes and lasts for several hours.
   d. Increase K excretion.
      i. Loop or thiazide diuretics: need to ensure adequate Na intake for response.
      ii. Cation exchange resins: **Sodium polystyrene sulfonate 15 to 30 g PO or by retention enema** exchanges potassium for sodium in the stool and induces osmotic diarrhea if given with sorbitol. May repeat every 4 to 6 hours as needed. Use cautiously in patient with impaired bowel motility (risk of colonic necrosis).
      iii. Hemodialysis: Consider for severe hyperkalemia, especially in setting of renal failure. Can induce transient hypokalemia with risk of cardiac arrhythmia.

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59 Acute Kidney Injury in the Intensive Care Unit

Konstantin Abramov and Thejas N. Swamy

I. GENERAL PRINCIPLES

A. Definition.

1. Acute kidney injury (AKI), previously known as *acute renal failure* (ARF), is characterized by a sudden decline in kidney function. Most important features are azotemia (accumulation of nitrogenous waste products, e.g., urea and creatinine) and oliguria (decrease in urine output to <500 mL/day). New definitions of AKI, based on either reduction of glomerular filtration rate (GFR) or oliguria, are being developed (e.g., RIFLE criteria).

B. Classification.

1. Categorized according to pathophysiologic mechanism.
- **a.** Prerenal azotemia: impaired renal perfusion.
- **b.** Intrinsic or parenchymal AKI: injury to the renal parenchyma.
- **c.** Postrenal AKI: obstruction of the urinary tract.

C. Epidemiology.

1. AKI in the intensive care unit (ICU) setting affects up to 25% of patients and is associated with a high mortality rate.

2. AKI often develops as a consequence of the course or treatment of other disorders.

3. Ischemia is the most common cause of AKI in the ICU and is often etiologically multifactorial.

II. ETIOLOGY

A. Prerenal azotemia.
See Table 59-1.

B. Intrinsic AKI.
See Table 59-2.

C. Postrenal AKI.
See Table 59-3.

For discussion of selected syndromes, see Table 59-6.

III. PATHOGENESIS

For pathogenesis of selected syndromes, see Table 59-6.

TABLE 59-1 Causes of Prerenal Azotemia

Hypovolemia
Gastrointestinal losses
Vomiting or NG tube drainage
Diarrhea
Renal losses
Osmotic diuresis (hyperglycemia)
Diuretics
Skin losses
Burns
Excessive insensible losses (fever)
Hemorrhage
Translocation of fluid ("third spacing")
Postoperative
Pancreatitis
Reduced effective circulating volume
Hypoalbuminemia
Hepatic cirrhosis
Cardiomyopathy (cardiorenal syndrome)
Peripheral blood pooling (vasodilator therapy, anesthetics, anaphylaxis, sepsis, toxic shock syndrome)
Renal artery stenosis
Autoregulatory failure
Medications (NSAIDs, ARBs, ACEIs, pressor agents, etc.)

NG, nasogastric; NSAIDs, nonsteroidal anti-inflammatory drugs; ARB, angiotensin receptor blocker, ACEI, angiotensin-converting enzyme inhibitor.

A. Prerenal azotemia.

1. Arises from a reduction in renal blood flow from hypovolemia, reduced effective circulating volume, renal artery stenosis, or autoregulatory failure.
2. Reduced renal perfusion leads to intense conservation of solute and water. It is a functional condition that is rapidly reversible with correction of renal perfusion.
3. With reduced effective circulating volume or autoregulatory failure, renal perfusion is compromised despite a euvolemic or hypervolemic state. This may be due to loss of vascular resistance, low cardiac output, or dysregulation of intrarenal hemodynamics.

B. Intrinsic AKI.

1. Acute injury to renal parenchyma from nephrotoxic or ischemic insult, which is not immediately reversible due to damage to nephrons.
2. Acute tubular necrosis (ATN) is very common as renal medulla is extremely susceptible to injury due to relatively poor oxygenation. Ischemia is most common cause, but ATN may result from nephrotoxins or inflammation of the renal tubular epithelium/interstitium.
3. Intratubular obstruction: Drugs (acyclovir, methotrexate, oral sodium phosphate bowel preparation) or toxins (ethylene glycol, myoglobin) can precipitate in and obstruct the tubules.

TABLE 59-2 Causes of Intrinsic (Parenchymal) Acute Kidney Injury

Tubulointerstitial disease
Acute tubular injury (acute tubular necrosis)
Ischemic
Nephrotoxins:
  Radiocontrast
  Medications: aminoglycosides, cisplatin, amphotericin B, foscarnet
  Pigment: myoglobin (rhabdomyolysis), hemoglobin
Tumor lysis syndrome: direct toxicity from uric acid and phosphates causing diffuse nephronal microobstruction and tubular damage
Acute interstitial nephritis (AIN)
  Drug induced: NSAIDs; antibiotics, most commonly penicillins, cephalosporins, sulfas; allopurinol; thiazides
  Infections: Legionella, Epstein-Barr virus, cytomegalovirus, etc.
  Autoimmune diseases: sarcoidosis, Sjögren syndrome
Glomerular disease
  Nephrotic syndrome: minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy
  Nephritic syndrome: membranoproliferative glomerulonephritis, IgA nephropathy, Wegener granulomatosis, vasculitis
Vascular disease
  Thrombosis
  Thromboembolism
  Atheroembolism
  Vasculitis
  Microangiopathy
    Scleroderma
    Malignant hypertension
    Toxemia of pregnancy
    TTP/HUS
    Medications (cyclosporine, mitomycin)

NSAID, nonsteroidal anti-inflammatory drug; IgA, immunoglobulin A; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome.

TABLE 59-3 Causes and Pathogenesis of Postrenal (Obstructive) Acute Kidney Injury

Prostatic hypertrophy or tumor
Neurogenic bladder
  Diabetes mellitus
  Multiple sclerosis
  Paraplegia
Neoplasms involving the urinary tract, particularly bladder[a]
Nephrolithiasis (if solitary functioning kidney)[a]
Retroperitoneal fibrosis[a]

[a]Complete urinary tract obstruction will cause anuria. However, partial obstruction, even if severe, may not affect urine output.

4. Glomerular injury can cause predominantly proteinuria/nephrotic syndrome or hematuria/nephritic syndrome. Nephrotic and nephritic syndromes may overlap.
5. Vascular disease may present as thrombosis, thromboembolic occlusion, or inflammation.

C. Postrenal AKI.
See Table 59-3.

IV. DIAGNOSIS

A. Clinical presentation.

1. AKI in the ICU setting often presents with azotemia and/or oliguria. Oliguria may precede azotemia.

B. Differential diagnosis.

1. See Tables 59-1, 59-2, and 59-3 for differential diagnosis of AKI.

C. History and physical examination.

1. Assess volume status.
2. Identify nephrotoxic exposures or events.
3. Associated symptoms and signs (rash, arthritis, hemoptysis, fever, liver disease, bladder distention, prostatic enlargement, etc.).
4. Symptoms and signs of uremia (lethargy, nausea, anorexia, asterixis, myoclonus).
5. Establish acuity and chronicity of renal disease.

D. Laboratory studies.

1. Urinalysis.
   a. Dipstick test for blood and protein.
   b. Urine microscopy.
      i. Dysmorphic red blood cell (RBC) or RBC casts (glomerulonephritis).
      ii. White blood cell (WBC) casts (acute interstitial nephritis [AIN], pyelonephritis).
      iii. Eosinophils (AIN).
      iv. Fatty casts (nephrotic syndrome).
      v. Muddy brown or coarse granular casts (ATN).
   c. Urine chemistries.
      i. Urine sodium concentration (UNa) <10 mEq/L suggests prerenal azotemia.
      ii. Fractional excretion of sodium (FENa).

$$\text{FENa} = (\text{urine sodium}/\text{plasma sodium})/(\text{urine creatinine}/\text{plasma creatinine}) \times 100\%$$

      (a) Less than 1% suggests prerenal azotemia.
      (b) May be falsely elevated in setting of diuretic use.
      iii. Fractional excretion of urea (FEUrea).

$$\text{FEUrea} = (\text{urine urea}/\text{plasma urea})/(\text{urine creatinine}/\text{plasma creatinine}) \times 100\%$$

(a) Unaffected by diuretics and is typically <35% in prerenal azotemia.

d. Blood tests.
   i. Serum chemistry studies: electrolyte and acid–base abnormalities.
      (a) Hyponatremia/hypernatremia.
      (b) Hyperkalemia/hypokalemia.
      (c) Metabolic acidosis.
   ii. Complete blood count (CBC).
      (a) Anemia (multiple myeloma, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [TTP/HUS], chronic kidney disease).
      (b) Thrombocytopenia (TTP/HUS).
      (c) WBC differential (eosinophilia suggests AIN, atheroemboli).
   iii. Serologic tests: should be ordered when indicated.
      (a) Antinuclear antibody (ANA), anti–double-stranded DNA antibodies (systemic lupus erythematosus [SLE]).
      (b) Antineutrophil cytoplasmic antibody (ANCA) (vasculitis).
      (c) Hepatitis serologies (polyarteritis nodosa, glomerulonephritis).
      (d) Antiglomerular basement membrane antibody titer (Goodpasture syndrome).
      (e) Cryoglobulins, complement levels (postinfectious glomerulonephritis, SLE).

e. Radiologic studies.
   i. Renal ultrasound: noninvasive and rapid; can assess both renal parenchyma and collecting systems. Sensitive for urinary obstruction. Small renal size and increased cortical echogenicity suggest underlying chronic kidney disease.
   ii. Postvoid bladder ultrasound: Assess bladder emptying.
   iii. Renal duplex: Screen for renovascular disease and renal vein thrombosis.
   iv. Computed tomography: high resolution, carefully consider risk/benefits before use of radiocontrast in patients with AKI.
   v. Retrograde pyelography: Consider if urinary tract obstruction suspected.
   vi. Radionuclide renal scan: Assess renal perfusion as well as function.
   vii. Renal arteriogram: Consider if renal artery thrombus suspected.
   viii. Magnetic resonance imaging (MRI): high resolution, carefully consider risks/benefits before use of gadolinium due to risk of nephrogenic systemic fibrosis (NSF). NSF risk may be reduced with postexposure hemodialysis.

f. Renal biopsy: Consider if other studies do not identify cause of AKI, if confirmation of diagnosis needed before initiation of specialized treatment such as immunosuppressive medication, or if prognostic information needed.

V. COMPLICATIONS

A. See Table 59-4.

TABLE 59-4 Complications of Acute Kidney Injury

Electrolyte abnormalities
Metabolic acidosis
Volume overload
Uremia
Abnormal drug metabolism
Platelet dysfunction

VI. PROGNOSIS AND OUTCOME

A. Overall, the mortality rate from AKI ranges from 25% to 64%. Mortality reaches 70% for AKI combined with sepsis.

B. Nonoliguric AKI is associated with the higher rate of recovery of renal function and approximately half the mortality of oliguric AKI.

C. Eventual recovery of renal function can be expected in most patients without prior chronic kidney disease who survive AKI.

VII. TREATMENT

A. See Table 59-5.

B. For treatment related to selected syndromes, see Table 59-6.

TABLE 59-5 General Management of Acute Kidney Injury

Weigh patient daily
Monitor input and output
Maintain mean arterial pressure (MAP) > 60–70 mm Hg and central venous pressure (CVP) 8–12 mm of water.
Consider diuretic challenge (furosemide 120–160 mg IV) for oliguric euvolemic patients; if no response, discontinue.
Restrict potassium intake (<2 g/d).
Consider supplemental bicarbonate for arterial pH < 7.2.
Discontinue and avoid nephrotoxins, if possible.
Adjust doses of all drugs excreted by the kidneys.
Avoid magnesium-containing drugs (antacids, milk of magnesia) due to the risk of hypermagnesemia.
Prerenal azotemia
  Correct volume depletion.
  Optimize hemodynamics.
Parenchymal
  Treat underlying illness.
  Maximize supportive care.
Postrenal
  Alleviate obstruction.
  Monitor for postobstructive diuresis.

The use of dialysis is discussed in depth in Chapter 60.

TABLE 59-6 Pathogenesis and Management of Selected Syndromes

Hepatorenal syndrome
- AKI in advanced liver disease, unresponsive to volume resuscitation
- Often precipitated by gastrointestinal bleeding, infection, diuresis, and large volume paracentesis (especially if done without concomitant albumin infusion)
- May be reversible with improvement in liver function or liver transplantation
- Management: midodrine (5–10 mg tid) in combination with octreotide (up to 250 μg SC bid); consider salt-poor albumin infusions (1 mg/kg/d up to a maximum of 100 mg/d for 48 h).

Cardiorenal syndrome
- Impaired renal perfusion due to low cardiac output
- Management: Treat underlying heart failure.
- Dialytic support if significant volume overload or poorly responsive to diuretics

TTP and HUS
- Characterized by microangiopathic hemolytic anemia, thrombocytopenia, and AKI. TTP, in addition, presents with fluctuating neurologic symptoms and fever.
- Causative factors: infection with *Escherichia coli* O157:H7, ADAMTS 13 deficiency, drug induced (quinine, mitomycin, cisplatin, antiplatelet agents, etc.), idiopathic in 40%
- Management: plasma exchange

Scleroderma renal crisis
- AKI with symptoms of malignant hypertension
- Occurs in 10%–20% of patients with systemic sclerosis
- Pathology: "onion skin hypertrophy" and intimal hyperplasia of interlobular and glomerular vessels. Urine sediment typically bland
- Management: ACE inhibitors; steroids contraindicated

Acute interstitial nephritis (AIN)
- Inflammation of the renal interstitium and tubules; often drug induced, with features of allergy: fever, rash, and eosinophilia (may be absent if NSAID induced)
- Treatment: If no improvement after drug withdrawal, consider prednisone 1 mg/kg/d for at least 1–2 wk (maximum of 40–60 mg/d), then taper gradually if serum creatinine is improving. Complete total course of 2–3 mo.

Myoglobinuric AKI
- AKI in setting of extensive myoglobin release from skeletal muscle injury (rhabdomyolysis)
- Serum creatinine phosphokinase > 10,000; urine dipstick strongly positive for blood without RBCs in urine sediment
- Management: initial volume expansion with 0.9% saline to maintain urine output 250–300 mL/h. Consider IV bicarbonate infusion (e.g., three ampules of bicarbonate in 1 L of 5% dextrose in water) in nonoliguric patients to keep urinary pH > 6.5 with close monitoring to prevent hypocalcemia or metabolic alkalosis. Give diuretics if volume overload develops.

(continued)

TABLE 59-6 Pathogenesis and Management of Selected Syndromes *(continued)*

Tumor lysis syndrome
- Diffuse nephronal microobstruction by released intracellular contents (phosphates, uric acid, purine metabolites) in setting of rapid cell death
- Diagnosis: high phosphorus, LDH, uric acid, potassium, and hypocalcemia
- Common precipitants: chemotherapy induction for hematologic and lymphoproliferative malignancies with large tumor burdens or for tumors with rapid cell turnover
- Management: volume expansion before chemotherapy, diuresis, pretreatment with allopurinol or rasburicase (recombinant urate oxidase enzyme) to prevent acute urate toxicity

Radiocontrast-induced nephropathy
- AKI develops within 24 h of radiocontrast exposure, peaks by 72 h, and improves over 4–7 d.
- FENa is <1%, high specific gravity, urinary sediment bland or with muddy brown casts
- Risk factors: preexisting renal insufficiency, volume depletion
- Risk can be reduced by preventive measures:
  1. 1 mL/kg of normal saline starting 2–6 h before the procedure and to continue for 6 h afterward or isotonic bicarbonate (D5W with 150 mEq of sodium bicarbonate 3 mL/kg/h 1 h before the procedure, then 1 mL/kg/h for 6 h after)
  2. *N*-acetylcysteine 600–1,200 mg every 12 h orally for two doses, before and after the procedure
  3. Use nonionic, low-osmolality radiocontrast and minimize contrast volume.

AKI, acute kidney injury; ACE, angiotensin-converting enzyme; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; ADAMTS, a disintegrin-like and metalloproteinase with thrombospondin; NSAID, nonsteroidal anti-inflammatory drug; RBCs, red blood cells; LDH, lactate dehydrogenase; FENa, fractional excretion of sodium; D5W, dextrose 5% in water.

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60 Dialytic Therapy in the Intensive Care Setting

Deep Adhikari and Dagmar Klinger

I. GENERAL PRINCIPLES

A. Background.

1. Dialytic therapy or renal replacement therapy (RRT) is essential for management of patients with end-stage renal disease (ESRD) and can be helpful for managing acute kidney injury (AKI) and toxic ingestions.
2. Different modalities of RRT include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and peritoneal dialysis (PD). Slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH) or hemodiafiltration (CVVHD), and slow low-efficiency dialysis (SLED) are different modalities of CRRT.
3. In IHD and hemofiltration, solute and water pass from blood into a solution (dialysate) across a semipermeable membrane within a filter (dialyzer). Blood is continuously pumped via a vascular access through an extracorporeal dialyzer circuit. The dialyzer membrane permits diffusion of small molecules and water into the dialysate compartment, while cells and large molecules are retained in the blood compartment. The blood pump generates a pressure gradient across the dialyzer membrane that removes volume through filtration of fluid.
4. In PD, solute and water diffuse from the blood across the peritoneal membrane into dialysate infused into the peritoneal cavity through a peritoneal catheter. After a period of equilibration, the initial dialysate is exchanged for fresh dialysate.

B. Mechanisms of solute, toxins, and fluid removal.

1. Diffusion: Solute or water moves from an area of high concentration (blood) to an area of low concentration (dialysate) through the dialyzer membrane. Diffusion is affected by concentration gradient, solute characteristics (molecular size and charge), dialyzer membrane characteristics (surface area, porosity, and thickness), and flow rate of blood and dialysate.
2. Convection: Solutes and water are forced across the dialyzer membrane by hydrostatic pressure. Filtrate has essentially the same chemical composition as plasma. Convection is most important for volume removal and hemofiltration.
3. Adsorption: Some substances (cytokines, antibiotics) may adhere directly to the dialyzer membrane. This process is limited by the binding capacity of the membrane and is of uncertain clinical significance.

C. Optimal modality, timing for initiation, and dosing of RRT for AKI remain controversial and guidelines are being developed.

II. INDICATIONS

A. Absolute indications.

1. Life-threatening fluid and electrolyte imbalances (hyperkalemia, hypervolemia, and metabolic acidosis) not amenable to other treatments.
2. Severe uremic symptoms (pericarditis, encephalopathy).
3. Life-threatening intoxication with a dialyzable substance.

B. Relative indications.

1. Minor uremic symptoms (nausea, lethargy, bleeding exacerbated by uremic platelet dysfunction).
2. Non–life-threatening chemical imbalances (moderate hypercalcemia).
3. Need for volume removal to allow for maximal medical therapy (enteral or parenteral nutrition).

III. TYPES OF RRT

A. IHD: the preferred method of RRT in hemodynamically stable patients.

1. Typically performed thrice weekly, but done more often if indicated.
2. Treatment duration is usually 3 to 4 hours; extended dialysis may be necessary for toxic ingestion (e.g., methanol).
3. Yields high solute clearance through diffusion and rapid fluid removal through convection.

B. CRRT: preferred for patients with significant hemodynamic instability, severe volume overload, and/or high obligatory daily fluid requirements. Hourly clearance is lower than IHD, but total daily solute and fluid removal typically greater.

1. SCUF: Ultrafiltrate is removed slowly, but not replaced. Used for fluid removal with minimal solute clearance.
2. CVVH: large volumes of ultrafiltrate (>1.5 L/hour) removed via convection and replaced with a physiologic crystalloid (replacement fluid).
3. CVVHD: combination of CVVH and IHD.
4. SLED: similar to IHD, but with much slower blood and dialysate flows conducted over a longer duration.

C. PD: used principally for ESRD and rarely for AKI because of difficulty in placing PD catheter and for potential impairment of pulmonary mechanics. Recent abdominal surgery is a relative contraindication.

IV. ACCESS

A. Vascular access.

1. Temporary.
   a. Dual-lumen venous catheter.
      i. Tunneled: preferred when the expected duration of RRT >3 weeks. Most commonly placed in right internal jugular vein.
      ii. Nontunneled: preferred for expected short duration. Access sites include internal jugular, subclavian (higher risk of central venous stenosis), or femoral veins (associated with increased infection rate when catheter is in place for >5 days). General guideline for catheter size.

(a) Left internal jugular: 11.5 Fr, 19.5 cm curved.
(b) Right internal jugular: 11.5 Fr, 13.5 cm curved.
(c) Femoral: 11.5 Fr, 19.5 cm straight.

2. Permanent.
   a. Arteriovenous fistula (AVF): preferred access for patients with ESRD. Surgical anastomosis of an artery and vein increases venous flow and causes enlargement (maturation) of the fistula over weeks to months. Not useful for AKI (prolonged maturation) or CRRT (risk of AVF rupture with prolonged needle cannulation).
   b. Arteriovenous graft (AVG): surgical placement of large-caliber synthetic conduit connecting an artery and vein. It can be used within 2 to 3 weeks. Not useful for AKI or CRRT.

B. PD catheters.

1. Temporary.
   a. Rarely used due to risks of catheter placement and infection.
2. Permanent.
   a. Soft, Dacron-cuffed catheters placed surgically; typically require 2 weeks to mature. Early use (with low dialysate volumes in supine patients) has high incidence of leakage from the catheter site.

V. ANTICOAGULATION:

to prevent clotting of the extracorporeal system during RRT. Avoid in patient with active or at high risk for hemorrhage.

A. Heparin: typically used with IHD. Generally given as a bolus with minimal postdialytic anticoagulant effect. Can be used for CRRT, but may have higher rates of filter thrombosis and bleeding complications than citrate. Contraindicated in heparin-induced thrombocytopenia (HIT).

B. Citrate: used extensively with CRRT. Regional anticoagulation achieved by calcium chelation and arrest of the coagulation cascade. This effect reversed by postdialyzer calcium infusion. Caution in liver disease (see Section VII.B.1.a.).

C. Prostacyclin: a short-acting agent that blocks platelet aggregation through arachidonic metabolite inhibition. Use limited due to hypotensive effect and cost.

VI. RRT FLUIDS

A. Dialysate solutions: The chemical composition closely resembles normal plasma, but does not contain metabolic waste products such as urea or creatinine.

1. Dialysate sodium concentration can be varied between 130 and 170 mEq/L (sodium "modeling" or "profiling") to minimize hypotension secondary to intracellular water shifts from acute reductions in plasma osmolality.
2. Dialysate potassium concentration is set based on plasma potassium level. Lower concentrations (1 to 2 mEq/L) remove more potassium, while higher concentrations (3 to 4 mEq/L) may replete potassium.
3. Bicarbonate concentration is typically 30 to 35 mEq/L to replete buffer.

B. CRRT replacement solutions.

1. Chemical composition is similar to dialysate.
2. Bicarbonate-, citrate-, or lactated Ringer–based solution used. Citrate may be limited by hepatic dysfunction (see Section V.2).

C. Peritoneal dialysate.

1. Contain various dextrose concentrations (1.5%, 2.5%, and 4.25%) to generate the osmotic gradient for diffusion of fluid. Higher concentrations increase solute and fluid removal.
2. Monitor serum glucose levels in diabetics.

VII. COMPLICATIONS

A. IHD.

1. Hypotension: common complication that can occur without volume removal due to water shifts induced by solute clearance. Can be partially prevented by cooling of dialysate (promotes vasoconstriction and improved myocardial contractility) and careful control of volume removal.
2. Dysequilibrium syndrome: neurologic symptoms, most commonly dizziness and headache, caused by transcerebral fluid shifts after dialysis. Can be avoided by limiting solute clearance during initial dialysis sessions.
3. Hypoxemia: due to alveolar hypoventilation and intrapulmonary leukostasis from cytokine release and complement activation triggered by reaction to dialyzer membrane. Clinically significant only in patients with severe cardiopulmonary disease.
4. Infection: due to either dialysis catheter or needle cannulation site infection or break in sterile technique.
5. Technical errors: air embolism and blood leaks rare with adequate precautions.
6. Hemorrhage: mandates a cautious use of anticoagulation.

B. CRRT.

1. Same as HD, except no dysequilibrium syndrome. In addition, issues related only to CRRT include:
   a. Hypocalcemia: Citrate is hepatically metabolized to bicarbonate and can accumulate in liver failure causing dramatic drop in ionized calcium despite normal or high total serum calcium due to chelation by citrate. Monitor both ionized and total calcium level regularly.
   b. Hypophosphatemia: phosphate clearance high with CRRT. Intravenous phosphate replacement usually required.
   c. Metabolic alkalosis.

C. Peritoneal dialysis.

1. Infection.
   a. Peritonitis from introduction of pathogens into the dialysis system during dialysate exchanges. Begin empiric therapy with vancomycin and ceftazidime pending culture results if suspected.
   b. Tunnel infections at the catheter exit site. May track into the peritoneum. *Staphylococcus aureus* and *Staphylococcus epidermidis* most commonly isolated. Gram-negative bacteria and fungi are occasionally culpable.

VIII. DISCONTINUATION OF DIALYSIS

A. Most patients with AKI become dialysis independent within several weeks. Signs of renal recovery include increased urine output in a previously oliguric patient and declining serum creatinine level between dialysis treatments.

B. Dialysis may also be discontinued if the goals of care become comfort only. Such end-of-life decisions should reflect close communication between patient (or their medical decision makers) and physicians.

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SECTION 6

Infectious Disease Problems in the Intensive Care Unit

Gail Scully

61 Approach to Fever in the Intensive Care Unit Patient

Sonia N. Chimienti and Richard H. Glew

I. GENERAL PRINCIPLES

A. Definition.

1. Normal average body temperature is 37.0°C (98.6°F); this may vary by 0.5°C to 1.0°C depending on time of day, activity level, and environmental and hormonal factors.
2. Fever in a normal host is defined as a single core temperature ≥38.3°C (≥101.0°F).
3. Fever in a neutropenic or otherwise immunosuppressed patient is defined as a single core temperature of >38.0°C (100.4°F) for >1 hour.
4. Hypothermia is defined as a temperature of <36.0°C in the absence of another explanation (cooling blanket, environmental, hypothyroidism).
5. The patient's overall clinical picture (e.g., trends in temperature, septic physiology) is more important than the absolute temperature.

B. Description.

1. Body temperature may be measured in a variety of ways.
   a. Pulmonary artery catheter thermistor most accurately assesses core body temperature, but generally is impractical.

b. Rectal temperatures are reliable but have some disadvantages.
  i. They may be perceived as invasive and uncomfortable by patients.
  ii. They may cause the spread of enteric pathogens (via the device or care provider).
  iii. They should not be used in neutropenic patients.
c. Oral temperatures generally are reliable and safe but also have disadvantages.
  i. They may be erroneous in patients who are mouth breathers.
  ii. They may be erroneous in patients who are not sufficiently alert to cooperate.
  iii. They may be erroneous in patients who just drank hot or cold liquids.
d. Axillary temperatures are less reliable and generally should not be used.

2. The febrile response may be blunted or absent in certain patient populations (i.e., the elderly, and patients with open abdominal wounds, azotemia, congestive heart failure, end-stage liver disease, large body surface area burns, and those who are receiving antipyretics or corticosteroids).
3. Environmental factors (i.e., specialized mattresses, hot lights, ambient temperature, continuous venovenous hemofiltration/continuous venovenous hemodiafiltration, peritoneal lavage) can influence a patient's measured body temperature.
4. Central and autonomic nervous system disruption can affect thermoregulatory responses.
5. Hypothermia may also be a sign of severe systemic infection.
6. Appropriate, timely, resource-conscious evaluation to determine the etiology of fever is important in order to initiate targeted treatment, to limit the utilization of laboratory tests, and to minimize the exposure of patients to unnecessary radiation and invasive procedures.

C. Epidemiology.

1. Fever is common in the ICU.
  a. May occur in up to one-third of hospitalized medical patients.
  b. May occur in up to 50% of ICU patients.
2. Fever in adult medical ICU patients is associated with increased mortality.
3. Rational and efficient evaluation of the etiology of fever is imperative.

II. ETIOLOGY

A. Common infectious causes of fever in the ICU.

1. Intravascular catheter-related bloodstream infections (CRBSI) (see Chapter 64).
  a. Risk of infection varies with a given device.
    i. Short-term, noncuffed central venous catheters (CVCs) (i.e., those used for hemodialysis)—2.7/1,000 catheter-days.
    ii. Peripherally inserted CVCs—2.1/1,000 catheter-days.
    iii. Arterial catheters—1.7/1,000 catheter-days.

iv. Surgically implanted long-term central venous devices.
(a) Cuffed and tunneled catheters—1.6/1,000 catheter-days.
(b) Central venous ports—0.1/1,000 catheter-days.
v. Small peripheral intravenous catheters—0.5/1,000 catheter-days.
vi. Midline catheters—0.2/1,000 catheter-days.

b. Consider endovascular focus (central venous septic phlebitis, endocarditis, graft infection) in the setting of persistent fever on effective antibiotic treatment, especially if positive blood cultures persist after removal of the implicated intravascular catheter.

2. Sinopulmonary infections (see Chapters 55 and 56).
a. Acute infectious pneumonia.
i. Severe community-acquired pneumonia (CAP).
ii. Ventilator-associated pneumonia (VAP).
iii. Health care–associated pneumonia (HCAP) in patients not ventilated.
iv. Aspiration pneumonia/pneumonitis.
b. Nosocomial sinusitis: Consider in patients with:
i. Transnasal intubation (prevalence of 33% after 7 days of intubation).
ii. Maxillofacial trauma with obstruction of nasal drainage.

3. Antibiotic-associated colitis (*Clostridium difficile* colitis) (see Chapters 76 and 79).
a. Causes 10% to 25% of all cases of antibiotic-associated diarrhea and almost all cases of antibiotic-associated pseudomembranous colitis.
b. May occur following treatment with virtually any antibiotic (most common precipitants are the fluoroquinolones, cephalosporins, and clindamycin).

4. Other gastrointestinal infections (see Chapters 80, 99, 100, 101 and 103).
a. Acute cholecystitis: calculous and acalculous.
b. Ascending cholangitis.
c. Diverticulitis, intra-abdominal abscess.
d. Mesenteric infarction.
e. Acute appendicitis.
f. Acute necrotizing pancreatitis.

5. Urinary tract infection (UTI) (see Chapter 65).
a. UTI is the most common nosocomial infection in the United States.
b. Catheter-associated UTI (CAUTI) in the ICU setting often due to nosocomial, multiple antibiotic-resistant gram-negative aerobic bacteria.
c. Candiduria associated with urinary catheters may represent colonization, but occasionally can be a clue to disseminated candidiasis in high-risk patients.

6. Skin and soft tissue infections.
a. Surgical site infections/wound infections.
i. Higher risk in certain patient populations (e.g., diabetic, immunocompromised), with emergent versus elective procedures and with prolonged surgical procedures.

ii. Most common etiologies are skin flora, including *Staphylococcus aureus*, including MRSA, and coagulase-negative *Staphylococcus* species.

b. Decubitus ulcers.

7. Central nervous system infections.

a. Uncommon causes of fever in ICU patients, in the absence of neurosurgical procedures, head trauma, high-grade bacteremia, invasive sinus infection, or immunocompromised state.

b. Patients with intracranial devices (shunt, ventriculostomy catheter, reservoir for chemotherapy) should have cerebrospinal fluid (CSF) sampling to rule out meningitis and determine the causative organism.

8. Others (consider seeding in the setting of persistent bacteremia).

a. Endocarditis.

b. Septic arthritis.

c. Osteomyelitis.

B. Common noninfectious causes of fever.

1. Drugs ("drug fever"); reactions to medications and blood products.

2. Postoperative fever.

3. Atelectasis.

4. Vascular.

a. Subarachnoid hemorrhage.

b. Cerebral infarction.

c. Dissecting aortic aneurysm.

d. Mesenteric ischemia (see Chapter 101).

e. Deep vein thrombosis (DVT) or pulmonary embolism (PE).

f. Acute myocardial infarction.

5. Malignancy.

a. Lymphoma.

b. Tumor lysis syndrome.

6. Endocrine/metabolic.

a. Hyperthyroidism/thyroid storm.

b. Adrenal insufficiency.

7. Others.

a. Seizures.

b. Pancreatitis (i.e., gallstone pancreatitis) (see Chapter 100).

c. Malignant hyperthermia/neuroleptic malignant syndrome.

III. PATHOPHYSIOLOGY

A. Principal mediators of fever: interleukin 1 (IL-1), tumor necrosis factor (TNF), and IL-6.

B. Cytokines interact with receptors in the anterior hypothalamic thermoregulatory area that releases prostaglandins, resetting the thermoregulatory set point.

C. Many aspects of ICU care can lead to impaired host defense and a resultant increase in the risk for infection (and thus fever), including:

1. Mechanical ventilation.

2. Indwelling intravascular catheters (arterial and venous) and urinary catheters.
3. Prolonged immobilization.

D. Expedient discontinuation of invasive monitoring and supports as soon as feasible prevents many nosocomial infections.

IV. DIAGNOSIS

A. Differential diagnosis.

1. Focus on the common infectious and noninfectious causes of fever noted above.

B. History.

1. If the patient cannot communicate, carefully review nursing and physician notes.
2. Pay particular attention to recent changes in clinical status, including:
   a. Decreased urine output or altered urine quality (cloudy urine, hematuria).
   b. Diarrhea or absent bowel movements.
   c. Requirement for increased ventilator support/oxygen requirement.
   d. Increased sputum production, increased endotracheal secretions, change in color/quality of endotracheal secretions.
   e. Difficulty infusing through CVCs in setting of new fever (consider line-related thrombus, infected or sterile).

C. Physical examination.

1. Conduct a thorough physical examination of all systems, with particular attention to the following:
   a. Entry sites of indwelling intravascular catheters (inflammation, purulent drainage).
      i. Consider duration of catheter cannulation.
   b. Oral or skin lesions/ulcerations, skin breakdown/pressure ulcers.
   c. Surgical wound sites.
   d. New or changing murmurs.
   e. Changes in the abdominal examination.
   f. Other indwelling catheters (urinary and peritoneal dialysis catheters, drainage tubes).

D. Laboratory studies.

1. The first episode of fever may be observed without additional evaluation if the history and physical exam do not suggest the presence of underlying infection.
2. Blood cultures should always be obtained to evaluate a new fever with a possible infectious etiology.
   a. Draw blood cultures before initiating empiric antibiotics, without significantly delaying treatment.
   b. Optimal yield of culture results to detect bacteremia or fungemia is achieved when two to three separate sets of blood cultures are obtained in the first 24 hours of a new fever evaluation.
   c. Separate sets of blood cultures should be obtained from different sites, by venipuncture through intact and noninfected skin.

3. Cultures of intravascular catheter tips (see Chapter 64).
   a. If a catheter is thought to be a source of infection, the device should be removed and the tip sent (in a dry, sterile container) for semiquantitative culture.
   b. If peripheral blood cultures are positive, catheter tip cultures positive with >15 colony-forming units suggest the catheter as the source of infection.
   c. A positive catheter tip culture with negative blood cultures may be of no clinical significance, unless the organism is a potentially virulent pathogen (esp. *S. aureus*), in which case treatment should be considered.
4. Sputum cultures.
   a. Most ICU patients become colonized in the oropharynx with gram-negative bacilli within a few days of hospitalization.
   b. Gram stain and culture of sputum/pulmonary secretions should be obtained, preferably before initiation of empiric antibiotics.
   c. Expectorated sputum or endotracheal aspirates.
      i. Adequacy of sample can be assessed by the presence of <10 epithelial cells and >25 polymorphonuclear cells per high-power field (nonneutropenic patients).
      ii. Recognition of a pathogen versus contaminant is suggested by the dominant presence of a recognized pulmonary pathogen versus the presence of multiple organisms in scant amounts on Gram stain and culture.
      iii. Semiquantitative culturing of endotracheal secretions appears to yield similarly useful clinical information as quantitative bronchoscopy.
   d. Fiberoptic bronchoscopy.
      i. Quantitative bronchoalveolar lavage or protected specimen brush cultures may be helpful in determining the presence of a true pathogen.
      ii. Bronchoscopy may be particularly useful when unusual pathogens are suspected or if the patient is immunocompromised.
      iii. Additional stains, antigen testing, and cultures of sputum and bronchoscopy samples should be obtained as indicated by the clinical situation.
5. Urine studies.
   a. Urinalysis (spun sample) and culture should be obtained in each case of suspected nosocomial UTI.
   b. Collection from catheterized patients.
      i. Fluid should not be collected from the drainage bag (high levels of bacteria can develop while urine is retained within the collecting bag).
      ii. A fresh specimen should be aspirated from the urinary catheter sampling port.
   c. A midstream, clean-catch urine specimen provides adequate sampling from patients without indwelling urinary catheters.
   d. Prompt processing is essential to prevent overgrowth of contaminating bacteria.

e. Growth of >100,000 colonies of a pathogenic bacterium likely represents true infection but lower colony counts can be significant in catheterized patients.

6. Cultures of fluid collections.
   a. Pleural fluid/thoracentesis.
      i. Send for Gram stain, aerobic and anaerobic culture, cytology, measurement of pH, protein, and glucose and lactate dehydrogenase (LDH).
      ii. Indicated in a febrile patient without another obvious source.
      iii. Should also be performed in individuals with trauma to the chest, recent thoracic surgery, or concern for a fistula.
   b. Surgical wound infections.
      i. Intra-abdominal collections must be sampled and drained, either percutaneously via interventional radiology or laparoscopy/laparotomy, depending upon the clinical situation and feasibility of each approach.
      ii. Incisional wound infections should be opened and cultured, irrigated, and left open with packing as indicated.
      iii. All collections should be sent for Gram stain and aerobic and anaerobic culture.

7. Stool studies.
   a. *Clostridium difficile* colitis must be ruled out in any ICU patient with fever, leukocytosis, and diarrhea, particularly in the setting of recent (within 60 days) antibiotic treatment, and should be considered in any such patient lacking an alternative explanation for fever.
   b. Stool cultures for common enteric pathogens should not be obtained routinely, *except* if a patient was admitted to the ICU with fever and diarrhea, and in immunocompromised patients.
   c. Stool ova and parasite examinations, cultures, or antigen tests for intestinal parasites should only be obtained in immunocompromised patients or in travelers recently returned from endemic countries.

8. Lumbar puncture.
   a. Consider in a patient with fever and any of the following:
      i. Sudden, unexplained change in mental status.
      ii. Recent history of head trauma or neurosurgery.
      iii. Mental status change that is difficult to evaluate.
   b. Basic evaluation: opening pressure, cell count with differential, glucose, total protein, Gram stain, and culture.
   c. Additional testing, depending on the clinical scenario (consultation with infectious diseases, neurology, or neurosurgery specialists is advised).

9. Biologic markers.
   a. C-reactive protein (CRP).
      i. Sensitive marker of sepsis, but not specific.
   b. Serum procalcitonin.
      i. Procalcitonin is released by cells in the setting of bacterial infection, within approximately 6 to 12 hours, via direct stimulation of bacterial cytokines.

ii. Procalcitonin is specific for bacterial infection versus viral infections or noninfectious inflammation.
iii. Procalcitonin decreases steadily in response to effective treatment of bacterial infection.
iv. Procalcitonin levels may be a useful adjunct to rule out infectious causes of fever and to limit use of antibiotics. For example, if a patient has a low procalcitonin level (<0.25 ng/mL), then it may be reasonable to withhold antibiotics and observe the patient clinically.
(a) In the ICU setting, use of procalcitonin levels to guide antibiotic initiation and de-escalation may decrease utilization of antibiotics by 20% to 37%.
(b) Cutoff values are not well defined, and algorithms for use of this marker are needed. In the ICU setting, a cutoff of 0.5 ng/mL has been used in some studies; higher levels are predictive of infectious causes of fever.
v. Procalcitonin levels might have increased utility when they are used together with disease severity scores, such as the APACHE III score and the simplified acute physiology score, or with other biomarkers such as CRP or serum lactate.

E. Radiologic studies.

1. Plain radiography.
   a. Portable upright anteroposterior chest radiography to rule out pneumonia.
   b. Posterior–anterior and lateral upright chest radiography is preferred, if feasible.
   c. Abdominal plain films for patients with abdominal distension, diarrhea.
2. Obtain more dedicated radiologic studies if initial films do not reveal a source.
   a. Chest computed tomography (CT) scan (noncontrast is sufficient to evaluate for parenchymal infiltrates, effusions, focal nodules, and masses).
   b. Dedicated CT scan of the sinuses to evaluate for opacification, mucosal thickening, air–fluid levels, and bony destruction is a more sensitive and specific test to rule out sinusitis, compared with plain radiographs.
   c. Abdominal/pelvic CT scans to evaluate for intra-abdominal collections/abscesses, colitis, neutropenic enterocolitis, diverticulitis, appendicitis.
   d. Immunocompromised patients may warrant earlier/aggressive radiologic evaluation.

V. TREATMENT

A. Principles.

1. Daily reassessment of all indwelling CVCs to determine if they are still necessary.
2. Avoid the femoral site for central venous catheterization whenever possible.

3. Prompt initiation of empiric, broad-spectrum antibiotic treatment in patients with fever and signs suggestive of systemic infection/sepsis.
   a. Delay in therapy may increase morbidity and mortality in patients with sepsis.
   b. Antibiotic selection should be individualized based on clinical assessment and available laboratory and radiographic data.
   c. Not all patients require immediate and broad antibiotic treatment.
      i. Patients with stable hemodynamics (no clinical evidence of sepsis) and no apparent source of infection upon initial assessment may be observed while the diagnostic evaluation proceeds.

B. Definitive care.

1. Initial empiric antibiotic choices should be reassessed daily and tailored immediately to target an identified focus of infection and/or infectious pathogen.
2. Infected collections must be drained.
   a. Surgical wound infections must be opened, drained, and irrigated.
3. Whenever feasible, indwelling intravascular catheters should be removed if they are determined to be a probable or definite source of infection.
   a. Removal is advocated strongly in patients with prosthetic heart valves or newly inserted arterial grafts, to minimize the risk for endovascular infection of these devices.
   b. Removal of all intravascular devices, with reinsertion at new sites under sterile conditions, should be considered in patients with sepsis or septic shock, evidence of disseminated intravascular infection, or those who are refractory to initial medical and supportive management.

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Excellent systematic review of published randomized controlled trials assessing the utility of procalcitonin in limiting antibiotic use and impacting mortality and clinical outcome. Worth reading to better understand the uses and limitations of this biomarker.

62 The Use of Antimicrobials in the Treatment of Infection in the Critically Ill Patient

Wayra Salazar-Moreno and David M. Bebinger

I. GENERAL PRINCIPLES

A. Make all reasonable attempts to arrive at a diagnosis for the syndrome encountered.

1. Clinical outcomes improve with targeted treatment for an accurate diagnosis.
2. Use clinical signs and symptoms to develop a differential diagnosis and predict morbidity.
3. Pursue diagnostic studies until an accurate diagnosis is identified.

B. Develop an empiric antimicrobial regimen based upon the differential diagnosis and predicted morbidity.

1. Isolated fever does not require empiric antimicrobial therapy. Patients with vital sign abnormalities have systemic inflammatory response syndrome (SIRS), which can be due to infectious or noninfectious etiologies.
2. Immunocompromised patients and those with signs of vascular collapse or organ dysfunction generally require empiric antimicrobial therapy.
3. Source control is required for optimal care.
a. Remove infected catheters and other nonessential foreign bodies.
b. Drain infected collections (e.g., empyema).
4. Promptly treat patients with sepsis and organ dysfunction with broad-spectrum antibiotics.
a. All patients at risk for *Staphylococcus aureus* disease should be treated empirically for methicillin-resistant *Staphylococcus aureus* (MRSA).
b. Antimicrobials directed against gram-negative organisms depend on the clinical setting where the infection was acquired, the anatomic site of infection, and local susceptibility patterns (i.e., your hospital antibiogram).
c. Syndromes with an identified source should prompt antibiotic treatment directed at likely pathogens causing the specific type of infection.

C. Dose antimicrobials properly to ensure adequate levels and minimize toxicity.

1. The initial dose should be adequate to reach therapeutic levels quickly, rarely requires dose modification for organ dysfunction, and may need to be increased in septic shock.

2. Modification of subsequent doses may be required in patients with renal or hepatic dysfunction depending on the antimicrobial used.
3. Prescribe with attention to other medications being administered as many antimicrobials have drug–drug interactions.

D. Address dose/duration of therapy on a daily if not a shift-by-shift basis.

1. Discontinue antimicrobials if a noninfectious etiology explains the encountered syndrome.
2. Narrow antimicrobials when a specific organism is isolated and when sensitivity test results become available.
3. Adjust dose as needed when renal or hepatic function changes.
4. Determine the duration of therapy according to established standards.
5. Always discontinue nonessential antimicrobials to prevent toxicity and drug resistance.

II. ETIOLOGY/DIAGNOSIS/TREATMENT

A. Table 62-1 lists commonly used antimicrobials in the ICU setting along with some of their important characteristics.

B. Table 62-2 contains many of the commonly encountered infectious agents in the ICU setting and their preferred drug regimen(s).

TABLE 62-1 Important Considerations of Selected Antimicrobial Agents

Broad-spectrum[a] agents with activity against *Pseudomonas aeruginosa*

Ceftazidime (class: cephalosporins) (R)	• Not active vs. organisms with extended spectrum β-lactamase (ESBL) and Amp C β-lactamases (*Enterobacter* species); gram-positive coverage is reduced. • Well tolerated, good CSF penetration
Imipenem–cilastatin (class: carbapenems) (R) Others in class: meropenem, doripenem	• Excellent activity against most species including anaerobes (except *Stenotrophomonas*, *Burkholderia*, *Aeromonas*) • Side effects include bone marrow suppression, hemolytic anemia, and seizures; <1% cross-reactivity with penicillin allergic patients is observed.
Levofloxacin (class: quinolones) (R), (I) Also in class: ciprofloxacin	• Overuse has led to widespread gram-negative resistance. • Has *Mycobacterium tuberculosis* (MTB) activity; use with caution in patients with suspected MTB
Piperacillin–tazobactam (class: penicillins) (R)	• A preferred empiric agent when broad-spectrum antimicrobial activity is needed and in empiric therapy for severe sepsis • Organisms harboring ESBL and Amp C beta-lactamases (e.g., *Enterobacter* species) are likely resistant.

TABLE 62-1 Important Considerations of Selected Antimicrobial Agents *(continued)*

Gram-negative agents with *P. aeruginosa* activity	
Amikacin (class: aminoglycosides) (R), (I)	• Used in combination with β-lactams to treat difficult infections; used empirically in septic shock when resistant gram-negative bacteria are suspected • Also active against some mycobacterial species • Lack of tissue penetration and renal and ototoxicity limit its use
Aztreonam (class: monobactams) (R)	• Active against aerobic gram-negative species but resistance is high in hospital strains of *P. aeruginosa*. • Reserved for use in patients with type I allergic reactions to β-lactams
Colistin (class: polymyxins) (R), (I)	• Reserved for multidrug-resistant gram-negative bacilli against which it has bactericidal activity • Use limited by dose-dependent nephrotoxicity, bone marrow suppression, neuromuscular blockade
Broad-spectrum[a] agents without *P. aeruginosa* activity (MRSA activity as indicated)	
Ampicillin–sulbactam (class: penicillins) (R)	• Preferred drug for human and animal bites; also community-onset head and neck infections • Typically active in community-onset oral and GI infections
Ceftaroline (class: cephalosporins) (R)	• Active against MRSA, resistant strains of pneumonococcus and gram negatives (not ESBL or pseudomonas) • Limited activity against anaerobes • Awaiting comparator studies to define its role in severe infections
Ceftriaxone (class: cephalosporins)	• Excellent broad-spectrum activity, use in combination with an anaerobic agent when anaerobes are suspected • Often the preferred empiric drug for serious pneumococcal infections (meningitis, pneumonia), other central nervous system, GI, and complicated urinary tract infections that arise outside the ICU • May cause biliary sludge/cholecystitis
Tigecycline (class: tetracycline) (H), (I)	• Broad spectrum with activity against some MRSA and vancomycin-resistant enterococci (VRE) species • Not active against *Proteus* and *Pseudomonas* species • Active against anaerobes, various aerobic gram-positive organisms, and many gram-negative organisms • FDA warns that mortality is increased in patients treated with this drug when compared to other agents.

(continued)

TABLE 62-1 Important Considerations of Selected Antimicrobial Agents *(continued)*

	Gram-positive agents
Cefazolin (class: cephalosporin) (R)	• Excellent drug for many soft tissue infections and severe methicillin-sensitive *Staphylococcus aureus* (MSSA) infections
Daptomycin (class: lipopeptide) (R)	• Active against gram-positive organisms but resistance has emerged on therapy. • *DO NOT* use to treat pneumonia as is inactivated by surfactant. • Muscle enzyme elevations limit higher doses that may be required to treat severe infections.
Linezolid (class: oxazolidinones) (I)	• Narrow-spectrum gram-positive agent active against both MRSA and VRE with good bioavailability and volume of distribution; resistance can develop on therapy. • Myelosuppression limits long-term use, usually after 2 weeks of therapy; neuropathy also occurs. • Serotonin syndrome observed with concomitant use of SSRIs
Oxacillin (class: penicillins)	• Preferred agent to treat serious MSSA infections and active against pen-susceptible streptococcal strains and gram-positive anaerobes but limited efficacy beyond these organisms • Side effects: allergic reactions, neutropenia, and elevated liver enzymes
Vancomycin (class: glycopeptides) (R)	• Preferred gram-positive agent for empiric therapy in severe infections • Given orally, it is the treatment of choice for severe *Clostridium difficile* colitis. • Rapid infusion results in histamine release, allergic reactions. • Bone marrow suppression and nephrotoxicity occur with high doses.
	Additional antibacterial agents
Ampicillin (class: penicillins) (R)	• Utility limited by β-lactamase production but used for susceptible enterococci, *Listeria,* gram-negative infections • Rash, allergy
Azithromycin (class: macrolides) (I)	• Use to treat atypical pulmonary pathogens (*Legionella* species, *Chlamydophila pneumoniae*, and *Mycoplasma*) • Active against some non-MTB mycobacteria
Metronidazole (class: nitroimidazoles)	• Excellent anaerobic activity; preferred treatment for mild *C. difficile* colitis • Well tolerated but has neurologic side effects including seizures and peripheral neuropathy

TABLE 62-1 Important Considerations of Selected Antimicrobial Agents *(continued)*

Trimethoprim–sulfamethoxazole (class: folate inhibitors) (R)	• Treatment of choice for *Pneumocystis jirovecii* and *Stenotrophomonas maltophilia* • Allergic reactions and GI upset are relatively common and bone marrow suppression is rare. • Use caution in renal insufficiency.
	Antifungal agents
Amphotericin B (class: polyene antifungals) (R)	• Treatment of choice for many severe life-threatening fungal infections (cryptococcal meningitis with flucytosine, zygomycosis) • Use is limited by significant toxicities, which are improved with lipid formulations but remain organ/life threatening.
Caspofungin (class: echinocandins) (H), (I)	• Used for empiric antifungal coverage in health care–associated infections
Others in class: micafungin, anidulafungin	• It is a second-line agent against *Aspergillus* species infections. • Mild side effect profile
Fluconazole (class: azole) (R)	• Well tolerated and effective agent against *Candida albicans* and other fungi including *Cryptococcus neoformans*
Voriconazole (class: azole) (R), (H), (I)	• Treatment of choice for invasive aspergillosis and active against *Candida* species; empiric therapy in patients with fever and neutropenia not responding to broad-spectrum antibiotics • Well tolerated but with visual side effects, sun sensitization
	Antiviral agents
Acyclovir (valacyclovir—oral)	• Used in *herpes simplex* virus infections; shingles in the immunocompromised host • Renal toxicity can occur due to crystal formation and reduced with adequate hydration.
Ganciclovir (valganciclovir—oral) (R), (I-CAUTION)	• Used for prophylaxis and treatment of cytomegalovirus in immunocompromised patients • Many side effects of which neutropenia is most significant; also reversible thrombocytopenia and nephrotoxicity • Used for resistant cytomegalovirus strains particularly in immunocompromised patients.

[a]Broad spectrum refers to having activity against many gram-positive, gram-negative, and anaerobic organisms.
(R), dose adjust with renal dysfunction; (I), significant drug interactions exist with this agent; CSF, cerebrospinal fluid; MRSA, methicillin-resistant *Staphylococcus aureus*; (H), dose adjust with hepatic dysfunction; ICU, intensive care unit; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor; MTB, *Mycobacterium tuberculosis*.

TABLE 62-2 Description and Treatment of Selected Intensive Care Unit Pathogens

Organism	Salient features and therapy
Acinetobacter species	Able to live on inanimate objects under stringent conditions. It is an opportunistic organism in hospitalized patients with the capacity to cause severe disease. Colonization and contamination should be considered with all positive cultures. Treat severe infections with two active agents. Local susceptibilities vary widely.
Aspergillus species	Highly prevalent fungus causing airway disease of various forms. It can produce hemorrhagic pneumonia characterized by vascular invasion. Definitive diagnosis requires biopsy; however serologic assays (e.g., galactomannan) are helpful in distinguishing colonization from infection. Treatment of choice is voriconazole.
Burkholderia cepacia	Hardy, resistant pathogen with ability to adhere to tissues and plastic, it also is invasive. Preferred therapy is TMP–SMX, but meropenem and minocycline are often active. Combination therapy recommended according to susceptibility profile in chronic lung disease patients
Candida species	Candidemia should be suspected in patients with risk factors (abdominal surgery, recent broad-spectrum antibiotics, indwelling catheters, and fungal colonization) who develop sepsis. Optimal treatment varies by *Candida* species but *C. albicans* usually susceptible to fluconazole.
Clostridium difficile	Causes diarrhea/colitis when overgrowth is permitted in the setting of antibiotic therapy due to toxin secretion. Stopping all unnecessary antibiotics can be curative. Severe disease: Treat with oral vancomycin. With GI motility disorder, add IV metronidazole. Colectomy may be required. Recurrent disease may require suppressive therapy or fecal transplantation.
Enterobacteriaceae species (*Citrobacter*, *Enterobacter*, *Serratia*, *Proteus*, *E. coli*, and *Klebsiella* species)	Widespread in environment and in human flora, involved in community and nosocomial infections. Resistance develops due to many mechanisms, and empiric therapy should be guided by local susceptibility patterns. Inducible β-lactamases are common in some species and expressed in response to antibiotic treatment.
E. coli, *Klebsiella* species	Can cause a host of infectious processes and can harbor a wide range of resistance mutations. Resistance to fluoroquinolones exceeds 40% in some ICUs. Empiric therapy depends on clinical factors and local susceptibility profile. Ceftriaxone is most likely adequate but any concern for ESBL production should prompt use of a carbapenem.

TABLE 62-2 Description and Treatment of Selected Intensive Care Unit Pathogens *(continued)*

Enterococcus species	Colonizes the GI tract of most humans. A frequent contaminant, it also causes severe disease including endocarditis. Bacteremia is associated with a poor outcome in ICU patients with or without effective treatment. Treatment depends on susceptibility testing; cell wall agent (penicillin or vancomycin) used with aminoglycoside for endocarditis. Vancomycin resistance require active agents such as linezolid, tigecycline, or daptomycin.
Legionella species	Thrives in warm water environments such as hot tubs and heating systems. May cause both CAP and HCAP. Treatments of choice are levofloxacin or azithromycin.
Listeria monocytogenes	Ubiquitous organism in the environment, disease (bacteremia, meningitis) tends to be limited to those with T-cell impairment (pregnancy, the elderly, neonates, HIV, and transplant patients). Treated with ampicillin.
Neisseria meningitidis	Causes bacterial meningitis that may be fatal especially with even minor complement deficiencies. Penicillin G and ceftriaxone are preferred treatments.
Nocardia species	Causes pulmonary infections and brain abscesses, usually in immunocompromised hosts. Most species are susceptible to sulfonamides (sulfamethoxazole).
Pseudomonas aeruginosa	Ubiquitous organism in the environment and frequent colonizer, it also develops biofilms and is difficult to eradicate from foreign materials and diseased tissues. Treatment considerations begin with defining the isolate as a colonizing or infecting organism. Remove (preferred) or replace foreign bodies. Life-threatening infections require treatment with two agents until susceptibility is known, preferably based on institution antibiogram data, with a β-lactam and aminoglycoside. Development of high-grade resistance is common.
Staphylococcus aureus (MSSA)	Wide range of infections from impetigo to toxic/septic shock to endocarditis. Continues to cause significant morbidity and should be treated aggressively. Oxacillin is much more active than vancomycin and is preferred treatment.
Staphylococcus aureus (MRSA)	Isolates in the setting of an infection are typically viewed as pathogens and treated aggressively. Vancomycin is the treatment of choice for severe infections despite recognized decrease in efficacy. Necrotizing pneumonias due to MRSA should be treated with linezolid. Ceftaroline shows promise but has not been studied in severe infections.

(Continued)

TABLE 62-2 Description and Treatment of Selected Intensive Care Unit Pathogens *(continued)*

Stenotrophomonas maltophilia	Able to withstand cleaning products and resistant to many drugs, it can colonize diseased tissue and cause catheter-related bacteremia. TMP–SMX best agent for treating infections
Streptococcus pneumoniae	Major cause of both community- and hospital-acquired pneumonia as well as bacterial meningitis. Pen-resistant strains seen frequently but ceftriaxone resistance is uncommon and vancomycin resistance not seen. Empiric therapy depends on severity of infection.

ID, infectious diseases; ICU, intensive care unit; TMP, trimethoprim; SMX, sulfamethoxazole; GI, gastrointestinal; IV, intravenous; VRE, vancomycin-resistant enterococci; ESBL, extended spectrum β-lactamase; CAP, community-acquired pneumonia; HCAP, health care–associated pneumonia; HIV, human immunodeficiency virus; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

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63 Central Nervous System Infections

Heidi L. Smith

I. GENERAL PRINCIPLES

A. Central nervous system (CNS) infections of major interest in the intensive care unit (ICU) include:

1. Bacterial meningitis.
   a. Clinical hallmark is stiff neck secondary to inflammation of the leptomeninges.
   b. Usually also have alteration of cerebral function (meningoencephalitis).
2. Encephalitis.
   a. Disturbance of cerebral function in conjunction with cerebral spinal fluid (CSF) pleocytosis.

II. ETIOLOGY

A. Bacterial meningitis.

1. Community-acquired meningitis.
   a. *Streptococcus pneumoniae*: most common in all age groups.
   b. *Neisseria meningitidis*: peak incidence in teenage years, outbreaks.
   c. *Listeria monocytogenes*: infants (<3 months), older adults (>50 years), alcoholism, immunosuppression, general debility.
   d. *Haemophilus influenzae* type B: formerly the most common cause in young children.
2. Nosocomial meningitis.
   a. Skin or hospital flora: staphylococci, aerobic gram-negative bacilli.

B. Encephalitis.

1. Herpes simplex virus (HSV): most common; one of the few etiologies for which a specific anti-infective agent exists.
2. Other causes include arboviruses (West Nile virus), Rickettsiae (Rocky Mountain spotted fever), and spirochetes (Lyme disease, syphilis).

III. PATHOGENESIS

A. Mechanisms of pathogen entry.

1. Bloodstream.
2. Contiguous extension.
3. Viral reactivation (HSV).

B. Meningeal irritation causes headache and neck stiffness.
C. Metabolic and circulatory disturbances may cause altered mental status.

IV. DIAGNOSIS

Clinical evaluation should be expedited to avoid treatment delays. The goals are to recognize the diagnosis and define the likely pathogen.

A. History.

1. Consider CNS infection in any patient with altered consciousness.
2. Classical meningitis presentation is acute-onset fever with headache, photophobia, and/or stiff neck.
3. Alcohol use, previous head trauma, recent antibiotics, ill contacts, and immunosuppression influence risk, etiology, and yield of diagnostic tests.

B. Physical examination.

1. Nuchal rigidity and altered consciousness are suggestive, but not always present in meningitis.
2. Papilledema or focal neurologic deficits: delay lumbar puncture (LP) until mass lesion is excluded.
3. Petechiae: suggests meningococcal meningitis, but nonspecific.

C. Laboratory studies.

1. Blood cultures: Collect before initiation of antibacterial therapy!
   a. Positive in 30% to 80% patients with community-acquired meningitis.
2. CSF: Collect promptly, except when mass lesion suspected.
   a. Bacterial meningitis.
      i. White blood cell (WBC) count: typically >1,000 cells/mm^3, neutrophil predominance.
      ii. Glucose: <20 mg/dL highly suggestive; normal in up to 50% of patients.
      iii. Protein: usually >100 mg/dL.
      iv. Gram stain.
      v. CSF culture.
   b. Encephalitis.
      i. WBC count: generally lower than in bacterial meningitis, monocyte predominance.
      ii. Glucose: 40% to 50% of blood glucose level.
      iii. Protein: elevated but less markedly than in bacterial meningitis.
      iv. HSV polymerase chain reaction (PCR): may be positive even after several days of antiviral therapy.

D. Radiologic studies.

1. Bacterial meningitis.
   a. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) normal in 76% of cases.
   b. Generally reserved for immunocompromised patients and those with focal neurologic deficits, suspicion of mass lesion, or new deterioration of clinical status.

2. Encephalitis.
   a. CT or MRI recommended to evaluate for infarcts or mass lesions.
   b. Focal encephalitis, particularly involving temporal lobes, suggestive of HSV.

V. TREATMENT

A. Bacterial meningitis.

1. Corticosteroids.
   a. Dexamethasone (0.15 mg/kg IV every 6 hours for 2 to 4 days).
   b. Begin immediately before or simultaneous with first antibiotic dose.
2. Empiric antibiotics (doses shown for adults with normal renal function).
   a. Start as soon as possible: within 30 minutes of initial evaluation.
      i. If LP delayed, start therapy as soon as blood cultures obtained.
      ii. Narrow therapy once organism is identified, and, for *S. pneumoniae*, ceftriaxone susceptibilities are available.
   b. Community-acquired meningitis.
      i. All patients: ceftriaxone 2 g IV q12h.
         (a) Meropenem 2 g IV q8h is an alternative agent.
      ii. Add vancomycin 15 to 20 mg/kg IV q12h if gram-positive cocci *or* if no organisms seen on Gram stain.
      iii. Add ampicillin 2 g IV q4h if age <3 months or >50 years, immunosuppression, alcoholism, debilitation, or CSF Gram stain shows gram-positive bacilli.
   c. Postneurosurgical meningitis.
      i. Vancomycin 15 to 20 mg/kg IV q12h plus ceftazidime 2 g IV q8h.
   d. Patients with β-lactam allergies.
      i. Vancomycin plus fluoroquinolone or aztreonam for patients with serious documented allergies.
      ii. Add trimethoprim–sulfamethoxazole 5 mg/kg q6–8h if risk for *L. monocytogenes*.
3. Infection control.
   a. Droplet precautions until 24 hours after start of antibiotic (*N. meningitidis*, *H. influenzae*, or unknown pathogen).
   b. Chemoprophylaxis.
      i. *N. meningitidis.*
         (a) Indications: household and day care contacts, hospital staff intimately exposed to nasopharyngeal secretions (e.g., intubation, nasotracheal suctioning).
         (b) Drugs: rifampin, ciprofloxacin, or ceftriaxone.
      ii. *Haemophilus influenzae.*
         (a) Indications: household contacts, if household includes an unvaccinated child <4 years or an immunocompromised child of any age.
         (b) Drug: rifampin.

B. Encephalitis.

1. Empiric acyclovir (10 mg/kg IV q8h in adults with normal renal function) in all patients with encephalitis pending results of HSV diagnostic workup or alternative diagnosis.
2. Consider empiric doxycycline (100 mg PO q12h in adults) for patients with clinical suspicion of ehrlichial or rickettsial disease.

VI. COMPLICATIONS

A. Seizures: Anticonvulsant therapy should be instituted if needed.

B. Increased intracranial pressure—severe cases managed with mannitol or steroids.

C. Subdural empyema.

1. Purulent collection between dura and arachnoid membrane.
2. Rapid deterioration of patient with bacterial meningitis should prompt emergent MRI to evaluate.

D. Venous thrombophlebitis.

1. Signs and symptoms dependent on location of thrombus.
2. May include new focal neurologic defect, decreased level of consciousness, or cerebrovascular accident in a nonarterial distribution.

ACKNOWLEDGMENT

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64 Infective Endocarditis and Catheter-Associated Blood Stream Infections

Wayra Salazar-Moreno and Gail Scully

I. GENERAL PRINCIPLES

A. Definition.

1. Infective endocarditis (IE) is a microbial infection of any portion of the endothelial lining of the heart; a valve is the most common site.

2. The presence of a vegetation characterizes IE.

B. Classification.

1. Native valve endocarditis (NVE) often presents as either

a. Acute: fulminant presentation with abrupt onset of fever, leukocytosis, rapid valve destruction, and systemic toxicity. Most commonly due to *Staphylococcus aureus*, but can also be due to *beta*-hemolytic streptococci and other pathogens. Preexisting valvular disease is not required.

b. Subacute: Insidious onset of constitutional symptoms over weeks to months is common. Preexisting valvular heart disease is common (rheumatic, congenital, or degenerative). Classically due to viridans streptococci or other agents of relatively low virulence.

2. Prosthetic valve endocarditis (PVE).

a. Period of greatest risk within 3 months of surgery, but can occur anytime. Early infection most commonly due to staphylococcal species. PVE more than 12 months postoperatively has the same microbiologic etiology as NVE.

II. ETIOLOGY

A. Organisms.

1. *Staphylococcus aureus* is the most common cause of IE worldwide (31%) for both community-acquired and health care–associated infections. Coagulase-negative staphylococci (CNS) are common pathogens in PVE and occasionally cause NVE.

2. Viridans streptococci cause 17% of IE worldwide and include *Streptococcus sanguis*, *Streptococcus mitis*, *Streptococcus mutans*, and *Streptococcus bovis*. The latter is associated with colonic neoplasia and hepatic disease.

3. Enterococci are the cause of 10% of IE.

4. *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* (HACEK) group causes 2% of IE.

5. Culture-negative endocarditis constitutes 7% of IE in North America.
   a. Due either to prior antibiotic use or to unusual or noncultivatable organisms such as *Bartonella* sp., *Brucella* sp., *and Coxiella burnetii*. The microbiology laboratory should be consulted when such diseases are suspected.

B. Risk factors for IE.

1. The most common risk factor is degenerative valvular disease due to aging.
2. Injecting drug use (IDU): most common risk factor for right-sided IE, but left-sided IE occurs as well in this population.
3. Hemodialysis, HIV, diabetes mellitus, previous IE, and other structural heart disease.

III. PATHOGENESIS

A. Trauma to the valve results in the elaboration of a fibrin–platelet thrombus.

B. Transient bacteremia from a distant site of infection, indwelling catheter, injection drug use, etc. becomes trapped in the thrombus and multiplies, and a vegetation ensues.

C. Complications: incompetence due to valvular destruction and septic pulmonary emboli in right-sided IE when *S. aureus* is the etiologic agent. Congestive heart failure and systemic embolization leading to stroke and distant sites of infection in left-sided IE.

IV. DIAGNOSIS

A. The diagnosis of IE is based on history, physical examination, blood cultures, laboratory tests, and cardiac diagnostics.

B. The Duke criteria are the most commonly accepted criteria for the diagnosis of IE.

C. History.

1. Fever is present in 96% of patients with IE.
2. Anorexia, weight loss, malaise, and night sweats are common in subacute IE.
3. Symptoms of complications: stroke, congestive heart failure, septic arthritis, etc.

D. Physical examination.

1. Skin findings: splinter hemorrhages under the nail beds in 8%, Osler nodes (tender, bluish–purple nodular lesions on the pads of fingers or toes) in 3%, and Janeway lesions (painless, pink, macular lesion often on the palms or soles) in 5%.
2. New heart murmur in 48% of IE, worsening of previous murmur in 20%.
3. Splenomegaly in 11% of IE.
4. Look for signs and symptoms of heart failure, embolic events, and distant infection.

E. Laboratory studies.

1. Blood cultures: a minimum of three separate sets of blood cultures within a 24-hour interval.
2. In adults, 20 to 30 mL of blood, drawn from a single site, is needed for a single set (two bottles) of blood cultures.

F. Cardiac diagnostics.

1. An electrocardiogram is a simple test that can suggest perivalvular extension of infection in IE when PR prolongation or new heart block is found.
2. Echocardiography should be performed in all patients with a moderate to high likelihood of IE to look for a vegetation and to characterize valve function.
   a. Transthoracic echocardiography (TTE) has an overall sensitivity for vegetations of 30% to 63%. TTE has limited ability to detect valve perforations and abscess formation and is insensitive for IE involving prosthetic heart valves. Specificity is 98%.
   b. Transesophageal echocardiography (TEE) has a sensitivity of 85% to 95% overall, but is less sensitive for PVE as compared to NVE. TEE is superior to TTE for detection of perivalvular abscess. Consideration should be given to TEE when a patient with a negative TTE has a high clinical suspicion for IE or an abscess is suspected.

V. TREATMENT

A. Bactericidal antimicrobial therapy is generally administered for 4 to 6 weeks.

1. When evaluating possible subacute IE, immediate empiric therapy may not be necessary, and three sets of blood cultures prior to antimicrobials are important.
2. All doses below assume normal renal function and no antimicrobial allergies.
3. Empiric therapy awaiting cultures should cover staphylococci, streptococci, and enterococci. Vancomycin is an appropriate therapy in most instances at a dose of 15 to 20 mg/kg every 12 hours.
4. Consensus guidelines for antimicrobial therapy of IE have been published by the American Heart Association and other professional societies.

B. Methicillin-susceptible staphylococcal (MSSA) IE: nafcillin or oxacillin 2 g every 4 hours or 12 g over 24 hours IV. For PVE due to MSSA, rifampin is added for the duration of therapy, with gentamicin for the first 2 weeks (if the organism is susceptible to these drugs).

C. Methicillin-resistant staphylococcal (MRSA) IE: vancomycin 15 to 20 mg/kg every 12 hours with a goal trough of 15 to 20 μg/mL. For PVE due to MRSA, rifampin and gentamicin are utilized in the same manner as for MSSA IE (see above).

D. Viridans group streptococci IE therapy depends on the penicillin minimum inhibitory concentration (MIC) of the organism. If the MIC is ≤0.12 μg/mL, penicillin G (penG) 12 to 18 mU/day IV continuously or in six divided doses is given for 4 weeks or ceftriaxone 2 g once a day for 4 weeks. Gentamicin is added for 2 or more weeks when viridans streptococci have a higher MIC, depending on the MIC of the organism. PVE due to viridians streptococci is treated for 6 weeks, and gentamicin is added for 2 or more weeks depending on the MIC.

E. Enterococcal IE: if susceptible, ampicillin 2 g IV every 4 hours plus gentamicin (unless high-level resistance) 1 mg/kg/every 8 hours IV for 4 to 6 weeks. Ampicillin-sensitive, high-level aminoglycoside-resistant enterococcal IE is generally treated with ampicillin and ceftriaxone combination therapy.

1. Enterococci resistant to penicillin or patients allergic to penicillin: vancomycin plus gentamicin for 6 weeks. IE due to ampicillin and vancomycin-resistant organisms warrants infectious disease consultation.

F. HACEK group IE: ceftriaxone 2 g once a day for 4 weeks.

G. Surgical management of IE is of increasing importance.

1. Surgery indicated in
   - **a.** Acute regurgitation leading to moderate to severe heart failure.
   - **b.** IE complicated by new heart block, perivalvular abscess, valve leaflet perforation, or persistent positive blood cultures.
   - **c.** Recurrent embolization on appropriate antimicrobial therapy.
2. Surgery should be seriously considered in the following patients.
   - **a.** IE caused by fungal or highly resistant organisms.
   - **b.** Left sided IE with large mobile vegetations in excess of 15 mm.
3. Antimicrobial prophylaxis to prevent IE is indicated for all patients with previous IE, prosthetic heart valves or other prosthetic cardiac material, some congenital cardiac conditions, transplant valvulopathy, prior to certain dental procedures (not routine cleaning), and biopsy of the respiratory tract mucosa.

VI. CATHETER-ASSOCIATED BLOODSTREAM INFECTIONS

A. General principles of catheter-associated bloodstream infections (CA-BSI).

1. Most of the estimated 100,000/year CA-BSI in the United States are associated with a central venous catheter (CVC).
2. Risk of infection is associated with duration of catheter.
3. Routine change of catheters is not recommended; catheters should be removed when no longer needed.
4. Utilizing maximal barrier precautions and chlorhexidine for skin preparation during line placement can decrease the incidence of CA-BSI.
5. While the subclavian site is least likely to be associated with CA-BSI, the femoral site should be avoided if possible when placing a CVC.

B. Etiology of catheter-associated bloodstream infections.

1. Staphylococcal species are the most common cause of CA-BSI, both coagulase negative (31%) and *S. aureus* (20%). Patients undergoing hemodialysis via a catheter are at highest risk.
   a. Coagulase-negative staphylococci are a common contaminant of blood cultures, and interpretation can be difficult.
2. Gram-negative rods cause 25% to 30% of CA-BSI, with *Klebsiella* species, *Escherichia coli*, *Pseudomonas* species and *Enterobacter* species most frequent.
3. Enterococci account for 9% of CA-BSI.
4. *Candida* species cause 9% of BSI; parenteral nutrition is a particular risk factor.

C. Pathogenesis of CA-BSI.

1. Nontunneled catheters have a higher risk of infection than tunneled catheters.
2. Microorganisms gain access to the bloodstream via the catheter exit site or via contamination of the hub of the catheter during use.
3. Seeding of the catheter due to a bacteremia originating from a distant site or a contaminated infusate can occur but is less common.

D. Diagnosis of CA-BSI.

1. When CA-BSI is suspected, two sets of blood cultures should be obtained prior to antibiotics when possible. Although national guidelines suggest that one set of cultures be drawn from the catheter and one peripherally, at our institution, we draw both sets of cultures from peripheral blood as we have found that cultures drawn from existing catheters are often contaminated. We allow one set to be drawn from a catheter immediately after placement when contamination is less likely.
2. "Tunnel" infections present with redness, swelling, tenderness, and warmth over the tunneled portion of the catheter. Purulence is sometimes present. In the absence of a tunnel infection, most infected CVCs look fine to the naked eye.
3. The tip of a CVC removed with no suspicion of infection should not be cultured.

E. Treatment.

1. Surgically implanted, infected CVCs can be salvaged at times, unless the organism is highly pathogenic (e.g., *S. aureus*, *Candida* species, or *Pseudomonas* species) or unless the patient is septic, has septic phlebitis, has persistent bacteremia, or has a tunnel infection, in which case remove the CVC.
   a. Patients should be made aware that attempts to treat a CA-BSI without catheter removal may fail.
2. When attempting to treat CA-BSI without removing the catheter antibiotic, "lock" therapy should be considered, with high concentrations of antibiotic left to "dwell" in the catheter lumen(s) between uses.
3. Infected nontunneled catheters should be removed.

4. Empiric therapy for CA-BSI should include vancomycin and in most circumstances also an antimicrobial agent active versus pseudomonas such as ceftazidime, cefepime, piperacillin–tazobactam, or an antipseudomonal carbapenem.
   a. For patients at risk for candidemia, consideration should be given to adding an antifungal agent especially if the patient is receiving parenteral nutrition.
5. Duration of therapy.
   a. If there is prosthetic material in the circulation, therapy may need to be prolonged depending on the etiologic organism.
   b. Coagulase-negative staphylococcal CA-BSI are generally treated for 7 days if the catheter is removed and 10 to 14 days if salvage is attempted.
   c. Uncomplicated CA-BSI due to
      i. Gram-negative organisms are generally treated for 10 to 14 days.
      ii. *Candida* species are treated for 14 days from the day of the first negative blood culture; an ophthalmologic consultation is indicated.
   d. *Staphylococcus aureus* CA-BSI should have catheter removal.
      i. Ideally, a new CVC should not be placed until follow-up blood cultures have been negative for 72 hours.
      ii. IE as a complication of CA-BSI due to *S. aureus* is common. A short course (14 days) of therapy should not generally be utilized unless the patient has a negative TEE, follow-up blood cultures at 2 to 4 days are negative, and there is no implanted prosthesis and no metastatic site of infection. An infectious disease consultation is strongly recommended for all episodes of *S. aureus* bacteremia.

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65 Urinary Tract Infections

Heidi L. Smith

I. GENERAL PRINCIPLES

A. Urinary tract infections (UTIs) are the most common nosocomial infections in the United States; most are associated with indwelling urinary catheters.

B. Complications of UTIs requiring intensive care unit (ICU) admission can include pyelonephritis, urosepsis with bacteremia, and suppurative infections.

C. Distinguishing between bacterial or fungal colonization and invasive infection can be difficult in the ICU setting.

II. ETIOLOGY

A. Gram-negative bacteria are most commonly isolated in UTI.

1. *Escherichia coli* is the most common single cause.
2. Other Enterobacteriaceae (*Klebsiella*, *Citrobacter*, *Enterobacter*, *Serratia*) are also frequently isolated.
3. *Pseudomonas*, *Providencia*, and *Proteus* sp. are common catheter-associated organisms.

B. Gram-positive bacteria can sometimes cause UTI.

1. *Staphylococcus aureus* can be seen in the setting of bacteremia; extrarenal sources should be considered.
2. Enterococci (including vancomycin-resistant enterococci [VRE]) and nonaureus staphylococci can be seen in the elderly or in patients with structural abnormalities or indwelling catheters.

C. *Candida* species can cause UTI and occasionally ascending infection and fungemia.

III. PATHOPHYSIOLOGY

A. Non–catheter-associated UTI.

1. Ascending infection following contamination of the lower tract with enteric organisms from the colon is most common.
2. Virulence factors may aid adhesion (e.g., fimbrial adhesions in *E. coli*) or alter the urinary tract environment (e.g., urease production by *Proteus mirabilis*).
3. Host anatomic or functional abnormalities that interfere with normal urine flow or bladder emptying increase risk for UTI.

B. Catheter-associated UTI.

1. Frequent movement in and out of the bladder increases the risk of infection through the external surface of catheter.
2. Risk of infection through the internal lumen increases when a standing column of urine accumulates, collection bag is elevated, or the closed collecting system is disrupted.
3. Temporary obstruction of urine outflow due to kinking aids establishment of pathogens.

IV. DIAGNOSIS

A. Classical clinical presentation consists of dysuria and urinary frequency, with or without fever.

1. Elderly individuals may present only with fever or mental status changes; however, asymptomatic bacteriuria is also very common in the elderly. Caution must be taken to avoid prematurely attributing these symptoms to UTI.

B. Urinalysis aids in the differentiation of microbial colonization versus infection.

1. Urinary white blood cell count >5 cells per high-powered field is suggestive of infection, but is not diagnostic.
2. Chronically catheterized patients, however, may have chronic pyuria in the absence of infection.

C. Urine culture identifies the pathogen and provides antimicrobial susceptibilities to allow narrowing of therapy.

1. Culture of >100,000 colony-forming units of a single species is suggestive of infection, but is also not diagnostic.
   a. In symptomatic individuals with pyuria, lower bacterial counts should not be disregarded.
2. Urine should be collected from the urine port, not the drainage bag.
   a. In chronically catheterized patients, a sample from a newly placed catheter is helpful.
3. Sampling should include nephrostomy tube, if present.

D. Blood cultures should be drawn before antibiotics in any patient with signs of developing sepsis or suspicion of pyelonephritis.

E. Imaging (renal ultrasound or computed tomography [CT] scan) should be performed if patient fails to improve promptly.

V. TREATMENT

A. Bacterial UTI.

1. Obtain blood and urine cultures before empiric antibiotics.
2. Renal dosing adjustments are required with most antibiotics.
3. Empiric treatment of suspected gram-negative septic shock or urosepsis consists of:

   a. Dual therapy with a β-lactam (extended spectrum penicillin, third- or fourth-generation cephalosporin, carbapenem) plus an aminoglycoside (or a quinolone in settings where resistance to quinolones does not exceed 10%) in critically ill patients.
   b. Monotherapy (β-lactam or aminoglycoside) may be utilized for less severe infections without recent antibiotic use. Quinolone monotherapy can be considered in areas where quinolone resistance is <10%.
   c. Alternatives for coverage of gram-negative enterics in patients with β-lactam allergies include aztreonam, quinolones, and aminoglycosides.
4. If enterococci are suspected, ampicillin or vancomycin should be added.
   a. In patients known to be colonized with VRE, linezolid should be considered.
5. Sensitivity data from a patient's past isolate as well as local antibiotic-resistance patterns can guide empiric therapy.
6. Antibiotic spectrum should be narrowed once sensitivities are available.
7. Always remove catheter if no longer necessary.
   a. If a catheter has been present >2 weeks at the time UTI is diagnosed, the catheter should be changed.
8. Therapy may be switched from parenteral to oral antibiotics once the fever resolves.
9. Duration of antibiotics for a severe UTI requiring ICU admission is generally 2 weeks.
   a. Catheter-associated UTI, which develops in the ICU setting and responds promptly to therapy, may be treated for 7 days.

B. *Candida* UTI.

1. Candiduria is a common finding in ICU patients.
   a. Removal of urinary catheter may result in spontaneous clearance.
2. Colony counts and pyuria are not as helpful in distinguishing colonization from infection.
3. Candiduria in the setting of neutropenia or urinary tract surgical procedures generally requires treatment, even if asymptomatic.
   a. In other patients, treatment should be reserved for symptomatic infections.
4. Fluconazole is the drug of choice due to excellent urinary concentrations.
   a. Amphotericin B (nonliposomal), flucytosine, or possibly echinocandins may be used for fluconazole-resistant *Candida* species.
5. In catheterized patients, candiduria frequently recurs.
   a. Placement of new catheter or a temporary intermittent catheterization may decrease colonization.
   b. Amphotericin B bladder washes result in only transient clearing of candiduria.

C. Prevention of catheter-associated UTI.

1. Minimize the duration of catheterization.
2. Meatal care and/or topical antimicrobials are not effective.
3. Minimize trauma.
4. Avoid elevation of drainage bag.

VI. COMPLICATIONS

A. Most patients respond to prompt, appropriate antibiotic therapy within 72 hours. Failure to respond should prompt a search for urinary obstruction or suppurative complications.

1. Urinary tract obstruction may prevent drainage of infected fluid.
   - **a.** Intrinsic obstruction due to stones or strictures.
   - **b.** Extrinsic obstruction due to external compression by intra-abdominal masses.
2. Abscess formation may interfere with effective antibiotic penetration.
   - **a.** Renal cortical abscesses secondary to hematogenous seeding.
   - **b.** Renal corticomedullary abscesses secondary to ascending processes.
   - **c.** Perinephric collections can result from rupture of infrarenal abscesses.
3. Emphysematous pyelonephritis, most commonly seen in diabetics, may require surgical management.

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66 Toxin-Mediated Illnesses (Toxic Shock Syndrome, Tetanus, and Botulism)

Iva Zivna and Richard T. Ellison III

I. TOXIC SHOCK SYNDROME

A. General principles.

1. Toxic shock syndrome (TSS) is a toxin-mediated multisystem disease characterized by the acute onset of high fever, hypotension, diffuse macular erythroderma, mucous membrane inflammation, severe myalgia, vomiting or diarrhea, and altered consciousness without focal neurologic signs.
   a. It arises as a result of infection or colonization with toxin-producing strains of *Staphylococcus aureus* (*S. aureus*) or *Streptococcus pyogenes* (*S. pyogenes*, group A streptococcus). In the initial epidemic, 50% of cases of staphylococcal TSS occurred in menstruating women using tampons.

B. Pathogenesis.

1. Staphylococcal TSS is mediated by *S. aureus* exotoxins (e.g., TSS toxin-1) that act as superantigens capable of activating large number of T cells. Activated T cells then release massive amounts of cytokines that mediate the signs and symptoms of TSS. The pathogenesis of streptococcal TSS appears comparable although the precise toxins involved have not been as clearly defined.

C. Diagnosis.

1. Five clinical features are needed for the diagnosis of TSS:
   a. Fever.
   b. Mucositis (often with rash).
   c. Hypotension.
   d. Desquamation over the palms and soles, typically 1 to 2 weeks after the onset of illness.
   e. Evidence of multiorgan failure.
2. Additionally there should be evidence of *S. aureus* or *S. pyogenes* by Gram stain or culture from a wound, mucosal surface, or normally sterile body site. Blood cultures are usually negative in *S. aureus* TSS but are positive in streptococcal TSS.

D. Treatment.

1. Correct hypovolemic shock rapidly.
2. Surgical treatment of infected areas, drainage of abscesses, and removal of foreign bodies.

3. Empiric antibiotic therapy for presumed staphylococcal TSS must provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin is currently preferred. Alternatives include linezolid, daptomycin, or trimethoprim–sulfamethoxazole (this last agent is not reliably active for *S. pyogenes*). Patients with suspected TSS should receive clindamycin to suppress bacterial toxin production.
4. Intravenous immunoglobulin (IVIG) can be considered for severe cases.

II. BOTULISM

A. General principles.

1. Botulism is a rare but potentially life-threatening neuroparalytic syndrome resulting from the action of botulinum neurotoxins produced by *Clostridium botulinum* or other closely related anaerobic, spore-forming, gram-positive bacillus species.
2. The syndrome of botulism is characterized by acute onset of bilateral cranial neuropathies associated with symmetric descending weakness.
3. It occurs in five forms based on the route of toxin exposure.
   a. Foodborne botulism.
   b. Wound botulism (including botulism in intravenous drug users).
   c. Infant botulism.
   d. Adult enteric infectious botulism.
   e. Inhalational botulism (could occur if aerosolized toxin was released in an act of bioterrorism).

B. Pathogenesis.

1. Regardless of the route of entry into the body, botulinum toxin (types A, B, C, D, E, and G) disperses widely through the vascular system and acts at the neuromuscular junctions, where it inhibits release of acetylcholine at cholinergic synapses.

C. Diagnosis.

1. Key features of the botulism include:
   a. Absence of fever.
   b. Symmetric neurologic (cranial nerve and motor) deficits.
   c. No change in level of consciousness.
   d. Normal or slow heart rate and normal blood pressure.
   e. No sensory deficits with exception of blurred vision.
2. The diagnosis can be confirmed by detection of botulinum toxin in the patient's serum, feces, or food; culture of the organism from contaminated food or wound; or repetitive nerve stimulation.
   a. Routine laboratory studies are nonspecific.
   b. Testing for botulinum toxin should be coordinated with the state health department and Centers for Disease Control and Prevention (CDC).

D. Treatment.

1. Proceed with elective intubation when:
   a. Oropharyngeal paresis is present, due to risk of aspiration.

   b. Decrease in vital capacity over 4 to 6 hours.
   c. Clinical signs of respiratory fatigue at a vital capacity of 15 mL/kg.
   d. Vital capacity falls below 1 L.
2. Administer heptavalent antitoxin (A, B, C, D, E, F, and G) available from the CDC to neutralize any circulating toxin in the serum.
   a. Contact state health department and the CDC (404-639-2206 or 770-488-7100) to obtain antitoxin.
3. In foodborne botulism, remove the unabsorbed toxin from the gastrointestinal tract using a nasogastric tube for lavage and a cathartic or a tap water enema.
4. In wound botulism, treat with debridement and intravenous penicillin G as well as antitoxin. Penicillin allergic patients should receive metronidazole.

III. TETANUS

A. General principles.

1. Tetanus is a disease of the nervous system characterized by persistent tonic spasms with severe brief exacerbations. The disease results from the action of tetanospasmin, a potent neurotoxin produced by *Clostridium tetani*, a large, spore-forming, anaerobic gram-positive bacillus.
2. Spores of *C. tetani* are found worldwide in soil.

B. Pathogenesis.

1. After a puncture wound or laceration, spores inoculated deep into tissue convert to vegetative forms that proliferate under anaerobic conditions. The growing bacteria release tetanospasmin that interferes with neurotransmitter release at the motor end plates of skeletal muscles, the spinal cord, brain, and within the sympathetic nervous system.

C. Diagnosis.

1. The diagnosis is primarily based on clinical manifestations. There are three principal forms.
   a. Localized tetanus with muscle spasms limited to the site of injury.
   b. Cephalic tetanus with paralysis of the cranial nerves (trismus or risus sardonicus).
   c. Generalized form of the disease.
2. Serologic testing is of no value as disease is produced by toxin levels that are too low to induce an antibody response.
3. Routine laboratory studies are nonspecific.

D. Treatment.

1. Assess airway and ventilation.
2. Control the spasms and decrease muscular rigidity with benzodiazepines; add paralytic agents if necessary.
3. Administer human tetanus immunoglobulin.
4. At a different site, administer tetanus toxoid to induce protective antibodies.

5. Begin antibiotic active against anaerobic bacteria (e.g., metronidazole or clindamycin).
6. Surgically debride any wounds.
7. Use short-acting drugs to manage autonomic dysfunction.

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67 Infections in Immunocompromised Hosts

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THE FEBRILE, NEUTROPENIC PATIENT

I. GENERAL PRINCIPLES

A. Definition.

1. See also Chapter 61.
2. Fever in a neutropenic patient is a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) for ≥1 hour.
3. Neutropenia is an absolute neutrophil count (ANC) of <500 cells/μL *or* an ANC between 500 and 1,000 cells/μL that is falling.
4. Severe neutropenia is an ANC of ≤100 cells/μL.
5. Risk of serious infection increases with severity of neutropenia and as the duration of neutropenia exceeds 7 days.

B. Classification.

1. **Low-risk patients** (may be managed in an ambulatory setting initially).
   a. Expected duration of neutropenia of ≤7 days *and* no significant comorbidities.
   b. Relatively lower risk of complications from chemotherapy-induced neutropenia.
   c. Exclusion criteria: hypotension, pneumonia, dehydration, bleeding, diabetes, leukemia, neurologic changes, history of fungal infection in the prior 6 months.
2. **High-risk patients** (should be hospitalized for initial management).
   a. Patients with significant neutropenia (ANC ≤ 100 cells/μL) *or* anticipated duration of neutropenia of >7 days *or* significant medical comorbidities (i.e., age > 60, cancer not in remission, hypotension, altered mental status, evidence of pneumonia) or recent use of alemtuzumab.
   b. Higher risk of complications due to neutropenia.
   c. Hematopoietic cell transplant (HCT) recipients (particularly allogeneic or cord blood stem cell transplant [SCT]) and those receiving chemotherapy for acute leukemia are generally considered high risk for prolonged neutropenia and are managed in the inpatient setting.

C. Epidemiology.

1. An infectious etiology is found in only 20% to 30% of patients with neutropenic fever.
   a. Bacteremia is found in approximately 10% to 25% of patients with neutropenic fever.
   b. Eighty percent of organisms isolated are from the patient's own flora.
2. Gram-negative organisms, such as *Pseudomonas aeruginosa*, have historically been the most significant cause of infections in this population.
   a. Gram-positive organisms have become more prevalent recently, due in part to use of antimicrobial prophylaxis with fluoroquinolones at the onset of neutropenia.
   b. Resistant gram-positive organisms (i.e., methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant enterococci [VRE]) are increasingly isolated.
   c. Gram-negative organisms continue to cause substantial morbidity and mortality and must be covered with empiric antimicrobial therapy.

II. ETIOLOGY

A. See also Section I.C Epidemiology and Section III Pathophysiology.
B. The risk/timing of infection due to specific pathogens depends upon the duration of neutropenia.
C. Common sites of infection in neutropenic patients with fever include the lungs (25%), oropharynx (25%), skin including central venous catheter (CVC) sites (15%), perineum (5%), gastrointestinal (GI) and genitourinary sites (5%), and sinuses (5%).

III. PATHOPHYSIOLOGY

A. Underlying malignancies, and their associated deficiencies of neutrophils, T lymphocytes, and B lymphocytes, increase the risk of infections from fungal, intracellular, and encapsulated organisms, respectively.

1. Decreased antibody production, or impaired antibody-dependent cell-mediated cytotoxicity (ADCC), can be seen in multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and patients who have undergone splenectomy (see below, section on The Asplenic Patient). These patients have increased risk for infection due to encapsulated organisms, including *Streptococcus pneumonia, Haemophilus influenzae, Neisseria meningitides, Capnocytophaga canimorsus,* and *Babesia* spp.
2. Defects in cellular immunity can be seen in patients with lymphoma and those receiving high-dose steroids in chemotherapeutic regimens (see below). These patients have increased risk for infection due to intracellular pathogens such as *Listeria monocytogenes*, *Salmonella* spp., *Cryptococcus neoformans, Mycobacterium tuberculosis,* and *Pneumocystis jirovecii.*

B. Cancer chemotherapy is cytotoxic to bone marrow and to the GI tract.

1. Chemotherapy-induced mucositis breaks down the normal host barrier to invasive infections and causes seeding of the bloodstream with bacterial and fungal organisms.
2. Chemotherapy causes neutropenia of varying severity and duration and places patients at increased risk for potentially serious infections.
3. Chemotherapy also impairs the normal function of neutrophils.

C. Indwelling CVCs increase risk of bacteremia due to skin flora.

D. Prolonged neutropenia, acute leukemia, broad-spectrum antibiotics, corticosteroids, and total parenteral nutrition predispose patients to invasive fungal infections.

IV. DIAGNOSIS

A. Clinical presentation.

1. Fever may be the only sign of a serious underlying infection, as the typical signs of inflammation are often absent in neutropenic patients.
2. Consider sepsis in a patient with hypotension, confusion, hypoxemia, and tachypnea.

B. Differential diagnosis.

The approach to management of a patient with fever and neutropenia is to assume that infection is present and to cover the patient with broad antimicrobial therapy until fever and neutropenia both resolve (see Section V Treatment).

1. Noninfectious etiologies should be considered in the appropriate setting.

C. History: A thorough history must be obtained daily. Note the presence of any new complaints, including a detailed review of the following systems:

1. Neurologic: mental status changes or confusion, increased somnolence.
2. Ophthalmologic: tearing of the eyes, blurred vision, loss of vision, diplopia.
3. ENT: sinus pain, rhinorrhea.
4. Respiratory: cough, shortness of breath, new chest pain/discomfort.
5. GI: abdominal distension or pain, diarrhea, rectal pain or bleeding.
6. Skin: new lesions of any kind.

D. Physical examination.

1. A thorough physical examination must be performed initially and repeated daily, with special attention to the oropharynx, sinuses, optic fundi, perirectal region, lungs, skin, recent surgical wounds, and vascular catheter sites.
2. Signs of inflammation may be diminished in neutropenic patients.
   a. Fever may be absent or only slightly above baseline temperature.
   b. Erythema and induration may be minimal or absent in neutropenic patients.
   c. Abscess formation requires normal neutrophil function.

3. Head and neck.
   a. Conjunctival injection, tearing of one or both eyes, restricted mobility of extraocular eye movements, and eschar in nasopharynx may suggest invasive fungal infection involving the orbits and/or sinuses.
   b. Vesicles in the ear canal may indicate the presence of a herpesvirus infection.
4. Skin.
   a. Pain, tenderness, and/or drainage (if present) at CVC entry sites/tunnels suggests the presence of a catheter-associated infection.
   b. Skin lesions such as nodules, necrotic ulcers, and vesicles may be a sign of systemic fungal, bacterial, and viral infections, respectively.
   c. Necrotic skin ulcers are frequently a sign of serious systemic infection due to gram-negative bacteria (i.e., *P. aeruginosa,* a cause of ecthyma gangrenosum) or invasive molds (i.e., *Fusarium* spp. or Mucorales).
5. Lungs.
   a. Wheezing (focal or diffuse), rales, or rhonchi may indicate infection due to nosocomial or community-acquired bacterial, fungal, and viral pathogens.
   b. Noninfectious causes may mimic infectious causes.
6. Abdomen.
   a. Abdominal pain and distension may be minimal or absent in neutropenic patients.
   b. Diarrhea may be due to chemotherapeutic regimens or mucositis.
   c. Prominent abdominal findings may suggest the presence of neutropenic enterocolitis, *Clostridium difficile* colitis, or abdominal sepsis. Unusual organisms such as *P. aeruginosa* and *Clostridium perfringens or Clostridium septicum* must be considered.

E. Laboratory studies.

1. Initial diagnostic tests should include the following:
   a. Complete blood count (CBC) with differential leukocyte count and platelet count.
   b. Serum creatinine, electrolytes, hepatic transaminases, total bilirubin.
   c. Ideally, cultures of peripheral blood (at least two sets) should be sent before antibiotics are started.
   d. Urinalysis and urine culture should be sent; however, pyuria is usually absent.
   e. Sputum culture in patients who are able to produce sputum.
   f. Stool culture and *C. difficile* toxin assay in patients with diarrhea.
   g. Swab, aspiration, or biopsy of suspicious skin or mucous membrane lesions for smears, cultures (bacterial, fungal, and viral), and pathologic examination.
2. Definitive diagnosis may require histologic examination and special culture techniques of specimens obtained by tissue biopsy, bronchoalveolar lavage (BAL), GI endoscopy, surgery, or other invasive procedures.
3. Fungal antigen testing.
   a. Serum galactomannan assay.

i. Detects the presence of the *Aspergillus* galactomannan antigen, a component of the *Aspergillus* cell wall that is released during growth of fungal hyphae.
ii. A positive test is suggestive of invasive *Aspergillus* infection.
iii. Sensitivity is diminished in patients receiving prophylactic antifungal agents.
iv. Specificity is diminished (results may be falsely positive) in patients who are being treated with piperacillin–tazobactam and in various other settings (infection with *Fusarium* spp. and in patients with severe mucositis due to chemotherapy or graft-versus-host disease [GVHD] after HCT).
v. The test is perhaps most useful in terms of its negative predictive value.

b. Galactomannan testing of BAL fluid.
i. Increased sensitivity as compared with culture of BAL fluid.
ii. Higher cutoff threshold for a positive result (≥0.8) results in excellent sensitivity (86%) and specificity (91%).
iii. May be useful for rapidly establishing a diagnosis in a neutropenic patient with nodular infiltrates suspicious for invasive fungal infection.

c. Beta-D-glucan assay (1,3-beta-D-glucan).
i. Component of the cell wall of many fungal pathogens, including *Candida* spp., *Aspergillus* spp., *Fusarium* spp., *Trichosporon* spp., and *P. jirovecii.*
ii. Nonspecific test for invasive fungal infection.
(a) Sensitivity between 55% and 95% and specificity between 77% and 96%.
(b) With a cutoff value of 80pg/mL, the positive predictive value is approximately 87%; negative predictive value is approximately 97%.
iii. False-positive results may be seen in the setting of albumin infusion, use of intravenous immunoglobulin, and occasionally in the setting of hemodialysis.

F. Radiologic studies.

1. Chest radiograph (CXR) or computed tomography (CT) scan: Chest CT has increased sensitivity compared with CXR for the detection of infiltrates in neutropenic patients.
a. Focal or multifocal infiltrates suggest bacterial or invasive fungal pneumonia.
b. Diffuse interstitial infiltrates are more characteristic of viruses, *Pseudomonas jirovecii*, or noninfectious processes.
c. Cavitary and nodular disease can be associated with bacteria (e.g., *P. aeruginosa, Staphylococcus aureus*, anaerobes), *Nocardia* species, mycobacteria, *Legionella*, endemic or invasive fungi, and noninfectious processes.

2. Abdominal imaging if indicated.
a. Intravenous contrast may be necessary to evaluate for intra-abdominal pathology.
b. Abscess formation may be absent in neutropenic, immunosuppressed patients.

V. TREATMENT

A. Principles.

1. Neutropenia confers a high risk for life-threatening infections.
2. All febrile neutropenic patients should be treated with intravenous broad-spectrum antibiotics promptly, after appropriate culture specimens are obtained.
   a. Initiate empiric antibiotics as soon as possible after the patient's presentation for care, without unnecessary delay; delay in administration of antibiotics contributes to increased morbidity and mortality. A reasonable goal for administration is no longer than 60 minutes after initial presentation for care.
   b. Empiric therapy must not be delayed while diagnostic testing is obtained.
   c. Empiric therapy must cover *P. aeruginosa*, as increased mortality is related to uncontrolled infection due to gram-negative organisms.
3. Recommended *initial* empiric antibiotic regimens for high-risk patients should take into consideration local antibiotic resistance patterns of *P. aeruginosa* but could include one of the following options:
   a. Ceftazidime 2 g IV every 8 hours (if no localizing signs or symptoms).
   b. Cefepime 2 g IV every 8 hours (if no localizing signs or symptoms).
   c. Piperacillin/tazobactam 3.375 g IV every 6 hours (suspected oral, dental, intra-abdominal, or other polymicrobial or anaerobic infection).
   d. Aztreonam 2 g every 6 hours plus vancomycin 1 g IV every 12 hours (in patients with severe penicillin allergy).
   e. Imipenem 500 mg IV every 6 hours or meropenem 1 g IV every 8 hours (suspected extended spectrum β-lactamase–producing organism, based on hospital antibiogram or patient past history).
4. Vancomycin (dosed per hospital guidelines) should be *added* to any of the above empiric regimens, if there is a concern for bacteremia or sepsis due to *Staphylococcus* species or other gram-positive organisms, evidence for tunnel or entry site infection related to a CVC, presence of cellulitis on exam, or severe mucositis.
   a. Discontinue vancomycin after 3 days of empiric treatment, in the absence of a documented pathogen requiring vancomycin for treatment, unless it is being used in combination with aztreonam in a penicillin-allergic patient.
   b. Infuse the beta-lactam before vancomycin; vancomycin infusion requires at least 1 hour, and this will unnecessarily delay coverage of gram-negative pathogens.
5. An aminoglycoside is typically only added to one of the regimens above for targeted therapy of documented infection. Consult Infectious Diseases.
6. Consider adding antiviral therapy (acyclovir) at treatment doses, if mucocutaneous lesions suspicious for herpes simplex virus (HSV) or varicella zoster virus (VZV) infection are present.

7. Antifungal therapy should be added empirically for patients with evidence of sepsis or for those at increased risk for invasive mold infections.
8. Consider empiric antifungal coverage after 4 to 7 days of persistent fever.
   a. Infectious Diseases consultation is strongly advised to assist with the selection of the correct empiric antifungal agent.
   b. Patients who have received prophylaxis with an antifungal agent should receive empiric antifungal treatment with an agent from a different class.
   c. Patients with persistent fever and neutropenia who have not received fluconazole prophylaxis, and who have no risk factors for infection with filamentous fungi, may in certain circumstances be treated with fluconazole empirically.
   d. Patients who have received antifungal prophylaxis with fluconazole should receive empiric treatment with an antifungal that will cover resistant *Candida* spp.
   e. Patients who meet any of the following six criteria should be prescribed an antifungal agent that will cover *Aspergillus* spp. or other filamentous fungi:
      i. Colonization with filamentous fungi.
      ii. Corticosteroid use in excess of 1 mg/kg/d.
      iii. Prolonged neutropenia, in excess of 20 days.
      iv. Presence of pulmonary infiltrates suspicious for invasive fungal infection.
      v. Patients with acute myelogenous leukemia as the underlying malignancy.
      vi. Recipients of allogeneic SCTs.
   f. Antifungal dosing and route of administration depends upon patient factors such as renal and hepatic function and severity of mucositis. Consult with Infectious Diseases and refer to hospital and pharmacy guidelines when dosing antifungals. Regimens can include:
      i. Fluconazole (loading dose of 800 mg IV or PO once on day one, followed by 400 mg IV or PO once daily thereafter).
      ii. Voriconazole (loading dose of 6 mg/kg IV or PO every 12 hours on day one, followed by 4 mg/kg IV or PO every 12 hours).
      iii. Amphotericin B or a lipid formulation of amphotericin (3 to 5 mg/kg IV once daily of liposomal amphotericin).
      iv. Caspofungin (loading dose of 70 mg IV on day one, then 50 mg IV once daily) or micafungin (generally 100 mg IV once daily for candidemia; check hospital formulary dosing guidelines).
9. Removal of indwelling CVCs should be considered in cases of:
   a. Bacteremia due to *S. aureus*, vancomycin-resistant enterococci, *Pseudomonas* species, *Candida* species, *Corynebacterium jeikeium, Bacillus* species, and *Fusarium* species.
   b. Evidence of tunnel or exit site infection.
   c. The presence of septic thrombophlebitis.
   d. Persistent or recurrent bacteremia, regardless of the organism isolated.
10. All empiric antibiotics may be discontinued when fever resolves *and* the ANC > 500 cells/μL, in the absence of a documented infection.

B. Supportive care.

1. Hemodynamic monitoring and support should be provided as per ICU protocols.
2. Respiratory/ventilatory support should be provided as per ICU protocols.

C. Dosing guidelines.

1. Antibiotic dosing should be adjusted for renal and hepatic dysfunction.
2. Gram-negative antimicrobial dosing should be appropriate for coverage of *P. aeruginosa*.
3. Refer to hospital and published guidelines for dosing of all antibacterial, antifungal, and antiviral agents, given the presence of comorbidities in this patient population.

D. End points.

1. Empiric antibiotics may be discontinued when fever *and* neutropenia have resolved.
2. When a specific pathogen is identified, antimicrobial therapy may be tailored to that organism, but broad coverage of gram-negative pathogens (including *P. aeruginosa*) should be maintained until the neutropenia resolves.
3. Documented infection should be treated consistent with published guidelines and taking into account duration of neutropenia and recovery of host defenses. Consultation with an Infectious Diseases specialist is strongly advised.

E. Prognosis.

1. Untreated gram-negative sepsis in neutropenic patients confers mortality of 90%.
2. Mortality in febrile, neutropenic patients in the current era of empiric therapy is generally <15%, with specific numbers depending upon the patient population and timing to initiation of effective empiric antibiotics.
3. Mortality is increased in patients with multiple comorbidities.

THE ASPLENIC PATIENT

I. GENERAL PRINCIPLES

A. Definition.

1. Asplenia may occur as a result of:
   a. Surgical removal of the spleen (splenectomy).
   b. Congenital absence of the spleen.
   c. Atrophy of spleen as a result of repeated injury/infarction (i.e., sickle cell disease).
2. Functional asplenia/hyposplenism is a marked reduction of splenic function that may occur in the setting of:
   a. Splenic vein thrombosis.
   b. Hypersplenism in end-stage liver disease.
   c. Splenic sequestration crisis in sickle cell disease.
   d. Splenic infiltration due to tumors, sarcoidosis, amyloidosis.

B. Description.

1. Asplenic and functionally asplenic patients are at increased risk for fulminant sepsis or overwhelming postsplenectomy infection (OPSI).
2. OPSI has a mortality rate of 50% to 70%.
3. Prompt consideration and treatment of OPSI is critical to patient survival.

C. Epidemiology.

1. More than 50% of episodes of OPSI occur within the first 2 years after splenectomy.
2. OPSI is described more frequently in children than in adults, although the risk of overwhelming sepsis persists throughout life in asplenic patients.

II. ETIOLOGY

A. OPSI develops in the setting of infection with encapsulated organisms.

B. *Streptococcus pneumoniae* is the most common causative organism of OPSI, causing roughly 60% of all cases.

C. OPSI due to type b *H. influenzae* (Hib) is much less common and historically occurred primarily in children before the use of the conjugated Hib vaccine. Cases of invasive infection due to Hib are now seen in older patients with waning immunity or in nonvaccinated individuals.

D. OPSI due to *Neisseria meningitidis* is uncommon, due in part to the relatively low incidence of this infection.

E. Other less common etiologies.

1. *Capnocytophaga canimorsus* may be a cause of sepsis in asplenic patients, with the infection transmitted via dog bites or scratches.
2. *Salmonella* species, particularly in patients with sickle cell disease.
3. Other β- and α-hemolytic streptococci.
4. *Escherichia coli* and other Enterobacteriaceae.
5. *Bordetella holmesii* has been described as a cause of bacteremia, endocarditis, meningitis, and pneumonia, primarily in asplenic patients.
6. *Bartonella* infection may be more significant in asplenic patients.

F. Unusual pathogens.

1. Babesiosis: Asplenic patients may have higher-grade parasitemias and hemolysis and higher morbidity and mortality as compared with patients with intact splenic function. Persistent or relapsing infection is also seen in asplenic patients.
2. Malaria: Asplenic individuals may have prolonged fever and parasitemia and a slower response to therapy than patients with normal splenic function.
3. Human granulocytic anaplasmosis: Response to therapy and resolution of fever may be prolonged in asplenic patients.

III. PATHOPHYSIOLOGY

A. Normal splenic function is essential for the efficient clearance of encapsulated bacteria coated by opsonizing antibodies.

1. The spleen removes infected or abnormal erythrocytes via sinusoidal capillaries.

2. Mononuclear phagocytes within the spleen ingest opsonized circulating bacteria.

B. Splenic B lymphocytes produce opsonizing antibody that control bacterial infections.

IV. DIAGNOSIS

A. Clinical presentation.

1. Any patient with actual or functional asplenia who presents with fever must be managed aggressively to prevent the development of fulminant sepsis.
2. OPSI may progress in the space of hours to fulminant sepsis.
3. A short prodrome of fever may progress rapidly to hypotension, disseminated intravascular coagulation (DIC), altered sensorium, and cardiovascular compromise.

B. Signs and symptoms.

1. Symptoms may be minor and can include fever alone or with chills, headache, upper respiratory symptoms, abdominal pain, or diarrhea.
2. Patients may appear only mildly ill or may present in septic shock.
3. Manifestations of OPSI may include hypotension, tachycardia and tachypnea, altered sensorium, meningeal signs, petechiae, or purpura.

C. Differential diagnosis.

1. Meningococcemia/purpura fulminans.
2. Staphylococcal sepsis/staphylococcal toxic shock syndrome.

D. History.

1. Details regarding the timing of and reason for splenectomy should be obtained.
2. Details regarding etiology of functional asplenia should be obtained.
3. History of pre- or postsplenectomy vaccinations should be recorded.
4. Other immunocompromising conditions should be noted.
   a. History of malignancy (lymphoma), sickle cell disease, collagen vascular disease.
   b. Use of immunosuppressive medications.
5. See also Section IV.C in The Febrile Neutropenic Patient.

E. Physical examination.

1. Vital signs: presence of hypotension, tachycardia, tachypnea, and oxygen requirement.
2. Meningeal signs.
3. Skin findings suggestive of decreased systemic perfusion or DIC.
4. See also Section IV.D in The Febrile Neutropenic Patient.

F. Laboratory studies.

1. White blood cell (WBC) count may be elevated or decreased with a left shift; band forms and toxic granulations are usually present.
2. Howell-Jolly bodies and "pocked" red blood cells suggest splenic dysfunction.
3. Abnormalities of coagulation and thrombocytopenia may suggest DIC.

4. Blood cultures should be obtained immediately upon presentation and often turn positive within a few hours, in the absence of prior antibiotic treatment.
5. See also Section IV.E in The Febrile Neutropenic Patient.

G. Radiologic studies.

1. Imaging studies may be useful to determine a source of infection.
2. See also Section IV.F in The Febrile Neutropenic Patient.

V. TREATMENT

A. Principles.

1. Patients with splenic dysfunction usually have a dose of antibiotics available to self-administer in the setting of fever, pending immediate medical attention.
2. Antibiotics should not be delayed for culturing more than several minutes in patients with splenic dysfunction; timely administration of antimicrobials can be lifesaving.
3. Empiric antimicrobials in the acute care setting.
   a. Vancomycin + a third-/fourth-generation cephalosporin.
   b. Meningeal dosing should be provided if central nervous system (CNS) infection is suspected.
   c. Patients with a documented allergy to penicillins/cephalosporins: Levofloxacin 750 mg PO q24 h can be substituted for the beta-lactam antibiotic.
4. Tailor antibiotics based on exposures (i.e., history of dog bite) and culture results.

B. Supportive care.

1. The patient should receive aggressive fluid resuscitation and hemodynamic support.
2. Inotropic agents are often needed.
3. Ventilatory support may be necessary for hypoxemia and for airway protection.

C. Prognosis.

1. Mortality may reach 40%, even with expedient, appropriate antimicrobial therapy.
2. If antimicrobials are delayed, mortality may approach 70%.

INFECTIONS IN PATIENTS RECEIVING ANTI–TUMOR NECROSIS FACTOR THERAPY

I. GENERAL PRINCIPLES

A. Available tumor necrosis factor (TNF)-α inhibitors include infliximab (chimeric mouse/human monoclonal antibody), adalimumab, golimumab (human monoclonal antibodies), etanercept (soluble receptor fusion protein), and certolizumab pegol (PEGylated Fab fragment of a humanized monoclonal antibody).

B. Approved indications for use of TNF-α inhibitors include rheumatoid arthritis, Crohn disease, psoriasis, and seronegative spondyloarthropathies.

C. Infection risk tends to be higher with infliximab as compared with etanercept.
D. Clinical presentations of infections may be atypical and are often disseminated.
E. Infection risk tends to be highest in the first year after initiation of a TNF-α inhibitor.

II. ETIOLOGY

TNF-α inhibitors increase the risk of reactivation of a variety of infections, typically intracellular and opportunistic pathogens.

A. Mycobacteria: The incidence of tuberculosis (TB) is increased more than sevenfold in patients treated with infliximab. It is less frequently reported with etanercept.
B. Fungal pathogens: histoplasmosis, cryptococcosis, coccidioidomycosis, local and systemic candidiasis, aspergillosis, and sporotrichosis.
C. Bacterial pathogens: *S. pneumoniae, S. aureus* (i.e., septic arthritis), *E. coli, Salmonella* spp., *Proteus mirabilis,* and *L. monocytogenes* (meningitis and/or septicemia).
D. Viral pathogens: reactivation of herpesvirus infections, including VZV and cytomegalovirus (CMV) infections.
E. Opportunistic pathogens, such as *Nocardia* spp., *Toxoplasma gondii*, *Legionella* spp., and *P. jirovecii.*
F. Hepatitis B and C infections may reactivate in the setting of treatment with TNF-α inhibitors. A flare of transaminases can occur and may worsen after withdrawal of the TNF-α inhibitor treatment, producing a picture similar to an inflammatory immune reconstitution syndrome.

III. PATHOPHYSIOLOGY

A. TNF-α plays a key role in the activation of macrophages and phagosomes, differentiation of monocytes into macrophages, and recruitment of neutrophils and macrophages.
B. TNF-α plays a role in host immunity against many intracellular organisms and is involved in granuloma formation (see Section II Etiology).

IV. DIAGNOSIS

A definitive diagnosis must be sought in order to guide management of infection in this patient population, as the risk of complications from untreated infection is high.

A. History.

1. Patients initiated on therapy with TNF-α inhibitors are screened for latent TB and hepatitis B and hepatitis C virus infections. Results of this prior testing should guide workup and management of a febrile patient taking TNF-α inhibitors.
2. History of vaccinations should be obtained.
3. Epidemiologic history should be obtained, including personal, work and travel history, contact with animals, dietary habits, and hobbies (i.e., hunting, gardening).

B. Physical exam.

1. A thorough physical exam will help to determine sites of involvement of infection.
2. Abscess formation may not occur in patients treated with TNF-α inhibitors.
3. Typical signs of inflammation may be attenuated or absent.

C. Laboratory studies.

1. Routine laboratory studies including CBC with differential, creatinine, hepatic transaminases, total bilirubin, and alkaline phosphatase.
2. Serologic and PCR testing for hepatitis B and C (including hepatitis B surface antigen, hepatitis B virus [HBV] DNA, hepatitis C virus [HCV] RNA) to evaluate for reactivation, if indicated based on history and/or prior laboratory testing.
3. Herpesvirus testing as indicated (CMV PCR from serum, VZV direct fluorescent antigen detection of lesions).
4. Targeted antigen testing, based on history, clinical presentation, and epidemiology.
   a. Histoplasma urine antigen.
   b. Serum cryptococcal antigen.
   c. Legionella urine antigen.
5. Blood cultures: two sets.
6. Urinalysis and urine culture.
7. Stool culture for salmonella if indicated.

D. Radiologic studies.

1. Chest radiography, if suggestive of pulmonary infection, may guide further diagnostic evaluation, including bronchoscopy with BAL. Radiologic appearance of infection may be atypical (i.e., miliary pattern as opposed to cavitary lesions in the setting of *M. tuberculosis* infection).
2. CT scan of the chest and abdomen may reveal fluid collections or mass lesions that can be sampled for further diagnostic testing. Typical abscess formation and peripheral enhancement of collections may not be apparent.

V. TREATMENT

A. TNF-α inhibitors should be discontinued in the setting of active infection.
B. Bacterial infection/sepsis should be treated empirically as per published guidelines.
C. Definitive treatment of identified pathogens should be provided as per published guidelines and is beyond the scope of this chapter.

INFECTIONS IN PATIENTS UNDERGOING T-CELL IMMUNOSUPPRESSION

I. GENERAL PRINCIPLES

A. T-cell immunosuppression, used commonly in solid organ transplantation and HCT, is associated with an increased risk of opportunistic infections.
B. Agents affecting T-lymphocyte activity, such as fludarabine and anti–T lymphocyte antibodies, are among the most severe suppressants of cell-mediated immunity.

C. Calcineurin inhibitors (cyclosporine, tacrolimus), steroids, and mycophenolate mofetil all significantly inhibit T-cell function in transplant recipients.

D. Prevention and treatment of GVHD significantly impairs T-cell–associated immunity.

II. ETIOLOGY

A. Pathogens previously well controlled by the recipient's immune system may reactivate in the setting of impaired cellular immunity.

1. Herpes viruses: HSV, VZV, CMV, Epstein-Barr virus (EBV), and human herpes virus-6 (HHV-6).
2. Latent fungal infections: *T. gondii*, *Histoplasma capsulatum, Coccidioides immitis, Aspergillus* spp., and *Pneumocystis jiroveci.*
3. Latent parasitic infections: *Strongyloides stercoralis.*
4. Latent mycobacterial infection: *M. tuberculosis and* atypical mycobacteria.
5. Others: polyoma viruses (BK virus).

B. Opportunistic infections associated with defects in cellular immunity may be newly acquired and cause significant infections (nocardiosis, listeriosis, legionellosis).

C. Community-acquired respiratory pathogens can cause more severe infection patients with impaired cellular immunity.

1. Viruses: adenovirus, respiratory syncytial virus, parainfluenza virus, and influenza.
2. Bacterial pathogens: *S. pneumonia* and *P. aeruginosa.*

D. GI infections can be protracted and refractory to treatment.

1. Bacteria: *Salmonella* spp. and *Campylobacter jejuni.*
2. Parasites: *Cryptosporidium, Microsporidium, Isospora,* and *Cyclospora.*
3. *Clostridium difficile* colitis.

III. PATHOPHYSIOLOGY

A. Cell-mediated immunity involves activation of macrophages and cytotoxic T lymphocytes to fight infections due to intracellular bacterial pathogens and viruses.

B. Inhibition of cell-mediated immunity using immunosuppressive agents increases the risk of infection due to intracellular pathogens (see Section II Etiology) and viruses.

IV. DIAGNOSIS

A. History.

A detailed history of epidemiologic exposures will help narrow the differential diagnosis of infectious etiologies in patients taking T-cell immunosuppressive therapies.

1. Personal exposures: travel history (recent and distant), dietary habits, participation in outdoor activities (gardening, composting, hunting), and exposure to animals.

2. Substance abuse history, including use of marijuana.
3. Exposure to sick contacts.
4. Past medical history for comorbidities.

B. Physical exam.

A detailed, thorough physical exam will help guide laboratory and radiologic testing. See above, Fever and Neutropenia, Section IV.D.

C. Laboratory studies.

See above sections on Fever and Neutropenia, Section IV.E, and TNF-alpha inhibitors, Section IV.C; in addition.

1. Stool culture for *Salmonella*, *Shigella*, *Campylobacter*; stool ova and parasite examination; cryptosporidium antigen; *Giardia* antigen, as indicated.
2. Bronchoscopy with BAL or lung biopsy is indicated in patients with a nondiagnostic evaluation for pulmonary disease or lack of clinical improvement on initial empiric therapy of pulmonary disease.

D. Radiologic studies.

See above sections on Fever and Neutropenia, Section IV.F and TNF-alpha inhibitors, Section IV.D.

V. TREATMENT

A. Principles.

1. Clinically stable patients may in certain circumstances be observed off of antibiotics pending workup.
2. Patients with signs of systemic infection should be started promptly on broad-spectrum antibiotics, covering the most likely pathogen(s) based on the history, physical examination, and initial laboratory and radiologic testing.
3. Empiric antibiotic regimens for patients who appear critically ill should include:
   a. Ceftazidime 2 g IV every 8 hours (if no localizing signs or symptoms) *or*
   b. Piperacillin/tazobactam 3.375 g IV every 6 hours (suspected intra-abdominal or other polymicrobial or anaerobic infection) *or*
   c. Imipenem 500 mg IV every 6 hours (suspected extended spectrum β-lactamase–producing organism, based on hospital epidemiology or patient past history) *or*
   d. Aztreonam 2 g every 6 hours plus vancomycin 1 g IV every 12 hours (in patients with severe penicillin allergy).
4. Vancomycin (dosed per hospital guidelines) should be *added* to any of the above empiric regimens, if there is a concern for bacteremia or sepsis due to *Staphylococcus* species or other gram-positive organisms or prior history of MRSA infection. Vancomycin should be discontinued after 3 days of empiric treatment, in the absence of a documented pathogen requiring this agent for treatment, unless it is being used in combination with aztreonam for empiric treatment in a penicillin-allergic patient.
5. Include trimethoprim–sulfamethoxazole (dose 5 mg/kg q8h, based on the trimethoprim component) if *P. jirovecii* is suspected.
6. Include treatment of GI pathogens if indicated based on history and physical exam.

B. Dosing guidelines.

1. Response to therapy may be delayed, and duration of treatment may be prolonged in these patients. Infectious Diseases consultation is strongly recommended.
2. Dosing of immunosuppressive medications should be reduced if this can be done safely, as directed by the primary oncology or transplant team. Inappropriate reduction in immunosuppression may lead to rejection of a transplanted allograft.

C. End points.

Treatment should be tailored to pathogens identified during the course of the evaluation.

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68 Human Immunodeficiency Virus in the Intensive Care Unit

Aruna Sree and Raul Davaro

I. GENERAL PRINCIPLES

A. In the era of combined antiretroviral therapy (ART), the spectrum of patients with human immunodeficiency virus (HIV) infection admitted to the intensive care unit (ICU) falls into three general categories.

1. Acquired immunodeficiency syndrome (AIDS)–related opportunistic infections.
2. Complications related to ART.
3. Medical problems unrelated to HIV infection.

B. Respiratory failure has been the most common cause of ICU admission, both in the AIDS epidemic and in the ART era. The other causes include sepsis, neurologic disorders, and end-stage liver disease.

1. Bacterial pneumonias and acute respiratory distress syndrome (ARDS) are the most common cause of respiratory failure. Patients with AIDS may have more than one opportunistic infection simultaneously.
2. *Pneumocystis jirovecii* pneumonia (PCP) incidence has been declining since the introduction of ART, and obstructive airway disease is increasing.
3. Tuberculosis (TB), fungal infection, and noninfectious HIV–associated pulmonary disorders are other common complications in patients with HIV infection admitted to the ICU.

C. There is increased incidence of sepsis and sepsis-related mortality in the ART era.

D. HIV patients coinfected with hepatitis B or hepatitis C have more severe liver disease. End-stage liver disease is a leading cause of mortality in the coinfected patients, despite of their better immunovirologic status.

II. PNEUMOCYSTIS PNEUMONIA

A. Etiology.

1. Caused by soil-based fungus, *P. jirovecii.*
2. Distribution: worldwide.

B. Pathogenesis.

1. PCP almost always occurs in patients with absolute CD4 counts <200.

C. Diagnosis.

1. Patients with PCP complain of progressive dyspnea, nonproductive cough, and low-grade fever.
2. The physical examination often reveals tachypnea, crackles, and trending hypoxemia. Although unusual, PCP can sometimes rapidly lead to acute respiratory failure.
3. The classic radiologic pattern in patients with PCP is diffuse alveolar or interstitial pulmonary infiltrates; however, almost every conceivable radiographic pattern has been reported.
4. Definitive diagnosis is by identification of organisms in pulmonary secretions or lung tissue. Sputum induction has a sensitivity of 55% to 94%. If sputum is negative, then bronchoscopy with bronchoalveolar lavage (BAL) should be performed. BAL has a sensitivity of 89% to 98%.
5. The sensitivity of PCR for bronchoalveolar lavage appears to be high although the ability to distinguish colonization from disease is less clear.
6. 1,3ß-D-glucan (a component of fungal cell walls) may be elevated in patients with PCP, but the assay's sensitivity and specificity for establishing a PCP diagnosis are problematic because other fungal diseases can produce elevation.

TABLE 68-1 Treatment of Moderate to Severe PCP

Drug	Dose	Comments
Trimethoprim (TMP) sulfamethoxazole (SMX)	15–20 mg/kg TMP in three or four divided doses for 21 d	Drug of choice; toxicity includes rash, fever, cytopenias, hepatitis, pancreatitis, nephritis, hyperkalemia, metabolic acidosis, CNS reaction, toxic epidermal necrolysis, Stevens-Johnson syndrome, and anaphylaxis; adverse reactions occur in up to 80% of HIV-infected patients necessitating alternative therapy in up to 50%.
Pentamidine isethionate	3–4 mg/kg IV daily	Alternative therapy in patients with life-threatening reactions to TMP–SMX; adverse reactions to pentamidine include hypotension, cardiac arrhythmias, pancreatitis, hypoglycemia, hyperglycemia, hyperkalemia, hypomagnesemia, hypocalcemia, neutropenia, hepatitis, and bronchospasm.
Prednisone	40 mg PO bid on days 1–5, 40 mg PO daily on days 6–10, and 20 mg PO daily on days 11–20	Adjunctive therapy in patients with arterial oxygen pressure ≤70 mm Hg or A–a gradient >35 mm, with steroids, reduces the mortality.

D. Treatment (Table 68-1).

1. Trimethoprim–sulfamethoxazole (TMP–SMX) is the treatment of choice for moderate to severe PCP. TMP–SMX is dosed at 15 to 20 mg/kg/d of TMP in three or four divided doses for 21 days.
2. In patients with life-threatening reactions to TMP–SMX (Table 68-1), pentamidine isethionate is the preferred alternative therapy. Pentamidine is administered as a single daily dose of 4 mg/kg intravenously.
3. In patients with arterial oxygen pressure <70 mm Hg, or A–a gradient >35 mm, adjunctive therapy with steroids reduces mortality—give prednisone 40 mg PO bid on days 1 to 5, 40 mg PO daily on days 6 to 10, and 20 mg PO daily on days 11 to 20.

III. TUBERCULOSIS

A. General principles.

1. HIV increases the risk of developing active TB.
2. Drug-resistant TB is more common in patients with HIV.

B. Etiology.

1. Caused by infection with *Mycobacterium tuberculosis.*

C. Pathogenesis.

1. In patients with HIV infection, TB can occur as a reactivation of latent disease or from newly acquired infection.
2. HIV-positive patients with latent TB infection have a 7% to 10% annual risk for developing active disease.

D. Diagnosis.

1. Clinical features.
   a. Patients with high CD4 cell counts (>400/mm^3) tend to have similar presentations to those without HIV (upper lobe disease, low risk of extrapulmonary dissemination).
   b. Patients with AIDS tend to have disseminated disease with prominent constitutional symptoms.
   c. Sometimes patients may present with ARDS or sepsis syndrome with multisystem organ failure.
   d. Immune reconstitution syndrome (IRIS) or paradoxical reactions may occur within 2 to 3 weeks of starting anti-TB treatment in HIV patients.
2. Diagnostic procedures.
   a. Sputum and/or BAL fluid for acid fast bacilli (AFB) smears, nucleic acid amplification test, cultures, and sensitivity.
   b. Isolator blood cultures and tissue biopsy of the involved site especially in disseminated disease.

E. Treatment.

1. Isoniazid/rifampin/pyrazinamide/ethambutol. Duration of therapy 6 to 12 months.
2. Drug-resistant TB requires treatment for a period of 18 to 24 months.
3. For ART-naive patients, ART should be started within 2 weeks when the CD4 count is <50 cells/mm^3 and by 8 to 12 weeks for all others.

IV. CRYPTOCOCCOSIS

A. General principles.

1. Most common central nervous system (CNS) fungal infection in patients with AIDS.

B. Etiology.

1. *Cryptococcus neoformans* causes most cases worldwide.

C. Pathogenesis.

1. Cryptococcosis is the result of newly acquired primary infection rather than reactivation of previously acquired disease.

D. Diagnosis.

1. Presents as subacute meningitis or meningoencephalitis with fever, malaise, and headaches. Most patients are symptomatic for 2 to 4 weeks before seeking medical care.

a. Less common manifestations include lethargy, altered mental status, personality changes, memory loss, or seizures.

2. Classic symptoms and signs of meningitis such as neck stiffness and photophobia are usually absent.

3. Elevated intracranial pressure (opening pressure >200 mm H_2O) is present in >50% of the patients.

4. Poor prognostic factors are change in mental status on presentation, high cerebrospinal fluid (CSF) cryptococcal antigen titers, low CSF leukocyte count, positive blood culture, or hyponatremia.

5. CSF shows lymphocytic meningitis with a white blood cell (WBC) count of 100 to 200 cells/mm^3, protein is mildly elevated, and glucose is low.

6. Diagnosis is by identification of *C. neoformans* in the CSF by:

a. Staining and culture.

b. Cryptococcal antigen in CSF and/or serum.

E. Treatment.

1. Induction therapy with amphotericin B (0.7 to 1 mg/kg/d) once daily with or without flucytosine (100 mg/kg/d) in four divided doses for 2 weeks.

a. Consolidation therapy with fluconazole (400 mg/day) for another 8 weeks or until CSF cultures are sterile, then secondary prophylaxis.

2. Management of intracranial pressure.

a. In HIV-infected patients with cryptococcal meningitis, elevated intracranial pressure occurs in >50% of cases and can be reduced through percutaneous lumbar drainage or removing enough CSF to reduce the opening pressure by 50%.

V. TOXOPLASMIC ENCEPHALITIS

A. General principles.

1. Toxoplasmic encephalitis (TE) is the most common cause of focal neurologic disease in patients with HIV infection.

a. Multifocal lesions are more common than single lesions.
b. Typically occurs when CD4 count is <100.

B. Etiology/pathogenesis.

1. *Toxoplasma gondii* is an obligate intracellular parasite whose definitive host is the cat.

C. Diagnosis.

1. Clinical features include headaches, confusion, fever, lethargy, focal neurologic signs, and seizures.
2. Patients with TE show multiple contrast-enhancing intracranial mass lesions on computed tomography (CT) scan of the brain or magnetic resonance imaging (MRI). MRI with intravenous gadolinium has superior sensitivity than CT scan.
3. Definitive diagnosis is by demonstration of tachyzoites in biopsy specimen of the brain; biopsy is done only when there is no clinical and radiologic improvement after 2 weeks of presumptive treatment.
4. A negative serology for toxoplasmosis is unusual in patients with TE.

D. Treatment.

1. Pyrimethamine (200 mg oral loading dose followed by 50 to 100 mg orally per day) plus sulfadiazine (1 to 1.5 g orally every 6 hours) for 2 to 3 weeks.
a. In patients intolerant to sulfadiazine, clindamycin (450 to 600 mg orally or 600 to 1,200 mg IV four times a day) can be used with pyrimethamine.
b. Patients must be properly hydrated while using sulfadiazine to avoid crystalluria.
c. Folinic acid at a dose of 10 mg PO daily must be used along with pyrimethamine to avoid bone marrow toxicity.
d. In patients intolerant to the above regimens, atovaquone can be used as salvage therapy (1,500 mg oral twice daily or 750 mg orally four times a day) with either pyrimethamine or sulfadiazine.
e. In patients where oral regimens cannot be given, TMP–SMX at the dose of 6.6 mg/kg/IV/daily of TMP can be used.

2. Adjunctive therapy.
a. Corticosteroids to reduce the cerebral edema and sodium valproate for seizures.

3. All patients receiving empiric therapy should have follow-up imaging studies after 2 weeks of treatment. Patients with AIDS and TE who ultimately respond to therapy should exhibit a favorable clinical response within 14 to 21 days and a radiologic response in all lesions within 3 weeks.

VI. IRIS

A. General principles.

1. IRIS is a paradoxical worsening of underlying opportunistic infections in HIV patients initiated on ART.

B. Pathogenesis.

1. Restoration of CD4 and CD8 T lymphocytes and cytokine release caused by initiation of ART.
2. IRIS is more common when treatment-naïve HIV patients are started on ART near the time of diagnosis with an opportunistic infection and experience a rapid fall in HIV viral load.

C. Diagnosis.

1. Soon after ART is begun, the patient experiences clinical or radiologic deterioration caused by an exacerbation of preexisting opportunistic infection or with appearance of new lesions in a patient responding to treatment of opportunistic infections.
   a. Most common organisms include *Mycobacterium avium complex*, *M. tuberculosis*, and *C. neoformans*.
   b. Patients with active TB treated with antituberculous therapy and ART experienced a higher incidence of paradoxical reactions (fever, worsening or emergence of lymphadenopathy, pulmonary infiltrates, and pleural effusions) than HIV-infected patients with TB not treated with ART.

D. Treatment.

1. In most patients with IRIS, opportunistic infections improve with continuation of ART.
2. In cases where IRIS is life threatening, ART should be temporarily discontinued until the underlying infection is treated.
   a. In antiretroviral-naïve patients with active TB, it is recommended that ART be delayed until 4 weeks after initiation of antituberculous treatment if the CD4 cell count is above 50.
3. In severe cases, adjunctive therapy with steroids may be used.

VII. LACTIC ACIDOSIS

A. General principles.

1. Lactic acidosis is a life-threatening complication caused by mitochondrial dysfunction that occurs in HIV-infected patients receiving nucleoside reverse transcriptase inhibitors (NRTIs)–based therapy.

B. Pathogenesis.

1. Lactic acidosis is caused by mitochondrial dysfunction through inhibition of DNA polymerase gamma.
2. The combination of NRTIs with the highest risk of lactic acidosis is stavudine plus didanosine.
3. There are some reports of lactic acidosis associated with nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).

C. Diagnosis.

1. Patients with NRTI-induced lactic acidosis present with fatigue, weakness, weight loss, nausea, emesis, abdominal pain, exercise-induced dyspnea, and unexplained tachycardia and tachypnea.
   a. There may be associated polyneuropathy, pancreatitis, myositis, lipoatrophy, and cardiomyopathy.

b. Laboratory abnormalities include elevated lactate levels, pancreatic enzymes, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and prolonged prothrombin time.

D. Treatment.

1. Immediate discontinuation of NRTIs/offending agent(s).
2. Bicarbonate therapy and hemodialysis in severe acidosis.

VIII. HISTOPLASMOSIS

A. General principles.

1. Primary disease is limited to endemic areas. Reactivation may occur many years after travel or residence in endemic areas.

B. Etiology.

1. *Histoplasma capsulatum*: a dimorphic fungus.

C. Pathogenesis.

1. The CD4 T cell count generally dictates the form of histoplasmosis seen in patients with HIV infection.
a. Localized forms of disease are generally seen in those with a CD4 T-cell count >200 cells/mm^3.
b. Extrapulmonary disseminated forms of disease are generally seen in those with a CD4 T-cell count <100 cells/mm^3.

D. Diagnosis.

1. Clinical syndromes.
a. Pulmonary histoplasmosis: Forms include localized infiltrates, diffuse infiltrates, and chronic cavitary disease.
b. Acute progressive disseminated histoplasmosis: fever, malaise, cough, dyspnea, diarrhea, mucosal ulcers, cutaneous lesions, lymphadenopathy, hepatosplenomegaly, and hematologic abnormalities.
c. Subacute progressive disseminated histoplasmosis: In addition to the above features, gastrointestinal (GI) manifestations in the form of ulcerations of the intestines, endocarditis and infection of other vascular structures, CNS, and adrenal gland involvement can occur.

2. Radiographic features include diffuse interstitial or reticulonodular infiltrates and hilar or mediastinal adenopathy.
3. Microbiologic diagnosis by
a. Blood cultures (isolator tube), BAL, or tissue cultures.
b. Detection of histoplasma antigen in urine or blood.

E. Treatment.

1. Severe disseminated disease: amphotericin B 0.7 mg/kg IV every 24 hours or liposomal amphotericin B 4 mg/kg IV every 24 hours for 3 to 10 days or until clinical improvement followed by Sporanox (itraconazole) 200 mg PO bid for 3 to 6 months.
2. Less severe disease: itraconazole 200 mg PO tid for 3 days followed by 200 mg PO bid for 3 to 6 months.

IX. SECONDARY PROPHYLAXIS

A. Once patients start ART, they must receive secondary prophylaxis for opportunistic infections, until their CD4 cell count remains above 200/mL for at least 3 months.

X. ART IN THE ICU

A. General principles.

1. Physicians must be aware of available methods of administration, drug interactions, and adverse effects of antiretroviral drugs in patients receiving ART when admitted to the ICU.
   - **a.** Most antiretrovirals are available only in oral form with only zidovudine (intravenous) and enfuvirtide (subcutaneous) available in parenteral form. Although there are antiretrovirals available in liquid form, erratic oral absorption in critically ill patients may lead to subtherapeutic levels hastening development of antiretroviral resistance.
   - **b.** Drug–drug interactions can occur between PIs and other agents used in critically ill patients most commonly through inhibition or induction of the hepatic cytochrome P-450 system. Medications that are used frequently in critically ill patients, which can interact with PIs, include azoles, benzodiazepines, neuroleptics, and calcium channel blockers.
2. HIV patients who are ART naïve: There is no conclusive evidence supporting the initiation of ART in critically ill treatment-naïve patients.
3. HIV patients already on ART.
   - **a.** There is little consensus on what to do in terms of continuing the treatment, unless the admission is directly related to highly active antiretroviral therapy (HAART).

XI. HIV TESTING IN THE ICU

A. General principles.

1. Specific informed consent for HIV testing is required in all 53 US states and territories. In 34 states, no exceptions to this rule have been enacted to allow nonconsented HIV testing among patients who are incompetent. When caring for a critically ill patient who is unable to consent to HIV testing, physicians might order tests considered surrogate markers of HIV infection such as a CD4 cell count. The information obtained from a CD4 cell count in absence of HIV serology represents an unethical attempt to circumvent the law, and the results in patients acutely ill may be misleading.
2. HIV screening is recommended for all patients after notifying the patient that the test will be performed, unless the patient declines. General consent for medical care would be sufficient in States where written informed consent is not required for HIV testing. Limitations to this in the ICU setting include patient's mental status and various state laws regarding HIV testing.

XII. MORTALITY

Mortality is associated with low CD4 count, diagnosis sepsis, low albumin, and ventilator dependency. Mortality is not associated with initiation of HAART prior to ICU admission.

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69 Tuberculosis in the Intensive Care Unit

Michael D. Mancenido and Jennifer S. Daly

I. GENERAL PRINCIPLES

A. Worldwide, 1.7 to 2 million persons die each year from tuberculosis (TB).

B. The changing epidemiologic features and resistance patterns of TB make this disease more difficult to recognize and treat for all health care providers, including those in the intensive care setting.

C. Prompt recognition of TB and early institution of effective therapy will allow successful treatment of the patient and the prevention of transmission.

D. Most patients with localized disease who adhere to a full course of anti-TB therapy are cured.

II. ETIOLOGY

A. TB is usually a subacute or chronic illness caused by *Mycobacterium tuberculosis* (MTB), also known as an acid-fast staining bacillus (AFB).

1. MTB commonly infects the lung but may also cause disease in other organs of the body.

III. PATHOPHYSIOLOGY

A. Primary infection.

1. Usually asymptomatic: Tubercle bacilli gain entry into the lungs, and then are phagocytized by alveolar macrophages. In most patients, a localized inflammatory process occurs with the development of granulomas.

2. In some individuals, the bacilli multiply in the lungs and cause extensive regional lymphadenitis, which produces symptoms.

3. Primary infection may disseminate in the bloodstream and seed the central nervous system (CNS), liver, spleen, kidney, and other organ systems (rare in adults).

4. Tuberculin skin test (TST) usually becomes positive 2 to 10 weeks after the primary infection.

B. Latent TB.

1. Classically characterized by a positive TST and lack of symptoms or signs of active disease.

2. Interferon-γ release assays (IGRAs) using whole blood detect latent infection and may be used as an alternative to the TST particularly in

foreign-born persons who have had Bacillus Calmette-Guèrin (BCG) vaccine. The tests use antigens not present in BCG, so cross-reactivity is not observed.

3. Immunocompetent persons develop a granulomatous inflammatory process and usually control but do not eradicate MTB infection.
4. Chest x-ray (CXR) is normal.

C. Active TB.

1. Occurs in approximately 10% of immunocompetent individuals infected with MTB over their lifetime.
   a. Half of these cases develop within the first 1 to 2 years after infection.
   b. The other half may occur at any point during an individual's lifetime (reactivation disease).
2. Associated with classic symptoms of cough, hemoptysis, fevers, night sweats, and weight loss.
3. In patients with defects in cell-mediated immunity, the risk of progressive primary, reactivation, or disseminated disease is increased.
   a. The *annual* risk of developing active TB is 5% to 7% among human immunodeficiency virus (HIV)–infected persons with latent TB infection.
   b. These patients often have poorly formed granulomas, have higher AFB burden in tissues, and may have atypical presentations.

IV. DIAGNOSIS

A. Patients critically ill from TB often have predisposing risks and/or comorbidities.

1. High-risk patients.
   a. History of latent TB (by positive TST and/or IGRA) or prior active TB.
   b. Contact with known or suspected active TB case.
   c. Immigration from countries with a high incidence of TB.
   d. Presence of fibrotic lung lesions or upper lobe scarring.
   e. Advanced age.
   f. Alcohol or other drug use.
   g. Institutional exposure (i.e., correctional facilities, homeless shelters).
   h. Immunocompromised host (HIV infection, chemotherapy, immunosuppressive therapy following organ transplantation, or use of steroids or anti–tumor necrosis factor agents).
2. There can also be critical involvement of multiple organ systems.
   a. Lungs: respiratory failure from fulminant tuberculous pneumonia, life-threatening (severe) hemoptysis, or acute respiratory distress syndrome (ARDS).
   b. Cardiac: pericardial tamponade from pericardial TB.
   c. CNS: TB meningitis.
   d. Gastrointestinal (GI): TB enteritis and perforation, pancreatitis.
   e. Systemic: disseminated TB with hepatosplenomegaly and pancytopenia.

B. Chest radiograph or chest computed tomography (CT) is the primary diagnostic and screening test for active TB.

1. Immunocompetent patients with pulmonary TB usually have abnormal CXR or chest CT findings.
   - **a.** Primary or childhood TB: lower lobe infiltrate (Ghon focus) with ipsilateral hilar adenopathy (Ghon complex, especially in children).
   - **b.** Reactivation or adult pulmonary TB: fibrotic and/or cavitary infiltrates in the apical segment of the upper lobes, superior segment of the lower lobes.
   - **c.** Primary TB infections in adults may present with either classic "primary" or "reactivation" radiologic findings.
   - **d.** Disseminated (miliary) disease: diffuse nodules 1 to 3 mm in size.
   - **e.** Old disease: upper lobe parenchymal scars or calcified granulomas representing fibrotic foci of healed inactive TB.
2. Immunocompromised patients may have a normal-appearing CXR.

C. Detection of MTB: microscopy (smear) and culture.

1. Sputum microscopy (AFB smear).
   - **a.** The most important diagnostic tool.
   - **b.** Sputum samples positive by auramine-stained smear or Ziehl-Neelsen stain may be examined with direct nucleic acid amplification tests to distinguish MTB from nontuberculous mycobacteria.
   - **c.** AFB stains and cultures of gastric aspirates, other body fluids, and blood may be diagnostic *in the appropriate clinical setting*.
2. Culture.
   - **a.** Obtain sputum specimens, as well as infected fluids, blood, bone marrow, lymph nodes, and tissue biopsies (e.g., pleural and pericardial) for AFB culture.
   - **b.** Timing: MTB grows slowly but some laboratories use a radiometric assay to detect MTB within 2 to 6 days, and then identification may be done promptly with genetic probes (1- to 3-week turnaround time compared to traditional 4 to 8 weeks).
   - **c.** Susceptibility testing: may be available (within 1 to 3 weeks for AFB smear-positive sputum specimens) with direct susceptibility testing. Additional weeks needed if the laboratory sends isolates to a reference laboratory after initial isolation.
3. Characteristic histology and AFB staining on tissue biopsy.
4. Direct PCR testing of sputum coupled with a test for rifampin resistance is available and is being used across the world for rapid diagnosis.

D. A diagnosis of TB may be delayed if antibiotic treatment, especially with fluoroquinolones, is empirically given to patients with "community-acquired pneumonia" that later are found to have TB.

V. TREATMENT

A. Empiric initiation of four-drug combination therapy.

1. Isoniazid (INH), rifampin, pyrazinamide, and either ethambutol or streptomycin.

2. When the strain is known to be susceptible to all agents, the total duration of treatment is usually 6 months, with INH and rifampin being used throughout the course; pyrazinamide and ethambutol (or streptomycin) can be discontinued after 8 weeks.

B. If the medications cannot be orally administered.

1. INH may be given intramuscularly. Rifampin and streptomycin are available for IV use. Second-line drugs including fluoroquinolones (moxifloxacin and levofloxacin) may also be given IV.
2. Other agents should be given through nasogastric or gastric or jejunal tube if the oral route cannot be used.

C. In patients with renal failure.

1. INH and rifampin may be given at standard doses. Vitamin B_6, pyridoxine, 50 to 100 mg daily should be given to patient with renal failure who are on INH to prevent neuropathy.
2. Ethambutol, pyrazinamide, streptomycin, and the fluoroquinolones require dose adjustments based on creatinine clearance.
3. Pyrazinamide should be dose reduced or avoided in a patient requiring hemodialysis.

D. When the strain is known to be resistant to both INH and rifampin, usually therapy is required for at least 18 to 24 months, and consultation with specialists in the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is advised.

E. Failure to convert to a negative smear and/or culture after 3 months indicates treatment failure from either nonadherence or drug-resistant TB.

1. In general, never add a single new anti-TB drug to a failing regimen. All new anti-TB drug regimens should ideally contain at least two drugs to which the organism is susceptible based on *in vitro* testing.
   a. Improper drug regimens may promote the emergence of drug-resistant TB strains.
   b. Consultation with specialists is recommended for management of patients with apparent treatment failure.
2. In cavitary pulmonary TB, when cultures remain positive after 2 months into therapy, yet the organism remains susceptible to all drugs, therapy should be extended to 9 months.

F. After discharge from the hospital, consider referring the patient to an outpatient program with directly observed therapy (DOT) and notify the local public health authorities.

1. Cure rates of >95% can be achieved with a 6-month regimen among patients with drug-susceptible organisms.

G. Corticosteroids are indicated for all patients with tuberculous meningitis and tuberculous pericarditis.

H. Antiretroviral therapy (ART) is strongly recommended for all HIV-infected patients with active TB infection.

1. If the patient's CD4 count is <50, ART should be initiated within 2 weeks of starting TB treatment.

2. If the patient's CD4 count is >50, and depending on the severity of the patient's clinical status, ART should be initiated no sooner than 2 weeks and no later than 12 weeks after starting TB treatment.
3. Consultation with a TB expert is advised in selecting the optimal ART and TB regimen.

VI. COMPLICATIONS

A. Immune reconstitution inflammatory syndrome (IRIS): This syndrome is a transient, paradoxical worsening of the patient's condition with fevers, increasing lymphadenopathy, new infiltrates, pleural effusions, or ARDS.

1. It can occur after initiation of treatment for TB and/or the underlying immunodeficiency, such as occurs with the initiation of ART in HIV/acquired immunodeficiency syndrome (AIDS) patients.
2. In patients with suspected IRIS, drug-resistant MTB, febrile response to therapy, coinfection with nontuberculous pathogens, or other alternative diagnoses must be ruled out.

B. Infection control and respiratory isolation.

1. Major concern is to prevent nosocomial transmission. Guidelines from the Centers for Disease Control and Prevention and the Occupational Health and Safety Administration form the basis of infection control policy.
2. A high index of suspicion and early recognition are key to allow the appropriate use of respiratory isolation and prompt initiation of treatment.
   a. The infectiousness of TB begins to decrease within days of the initiation of effective therapy.
3. Respiratory precautions.
   a. Negative-pressure isolation rooms with at least six air changes per hour.
   b. The use of closed suctioning systems to avoid generation of infectious aerosols and the use of submicron filters for air exhausted from ventilated patients.
   c. Personal protective devices (N95 masks or personal powered respirators) are required for the health care workers who will be in contact with the patient.

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70 Severe Community-Acquired Respiratory Viral Infections

Iva Zivna and Richard T. Ellison III

I. HUMAN INFLUENZA AND AVIAN INFLUENZA (H5N1)

A. General principles.

1. Seasonal influenza is an acute febrile illness caused by either influenza A or B viruses that occur in outbreaks of varying severity every winter season.
2. Highly pathogenic avian influenza virus A (H5N1) is a new influenza strain now endemic among bird and poultry population in Eurasia that rarely causes human disease. A second avian influenza A (H7N9) causing human disease has now been identified in China, and future avian influenza A strains are likely to emerge.
3. Suspect avian influenza (H5N1 or H7N9) infection in a patient who has traveled in an H5N1- or H7N9-affected country within 10 days of symptom onset and develops an acute respiratory distress syndrome (ARDS) or other severe respiratory illness for which an alternate etiology cannot be established.
4. Secondary bacterial pneumonia (often due to *Staphylococcus aureus, Streptococcus pneumoniae*, or *Haemophilus influenzae*) is an important complication of influenza infection and needs to be considered when exacerbation of fever and respiratory symptoms occurs after initial improvement.

B. Pathogenesis.

1. Human cases of H5N1 and H7N9 influenza have almost exclusively occurred after direct exposure to infected birds, with viral replication occurring in the retropharyngeal area and lower respiratory tract.
2. Uncomplicated illness usually resolves in 2 to 5 days. The predominant complication is superimposed bacterial pneumonia. Rare complications include myositis, myocarditis, encephalitis, and Guillain-Barré syndrome.

C. Diagnosis.

1. Acute febrile illness with malaise, myalgias, headache, and upper and lower respiratory tract symptoms in appropriate epidemiologic setting.
2. Routine laboratory studies are nonspecific.
3. Molecular techniques (e.g., polymerase chain reaction [PCR] assay).

4. Diagnosis can be confirmed by detection of virus or viral antigen or fourfold or greater rise in specific antibody titers.
5. Growth of the H5N1 or H7N9 viruses should only be attempted in a biosafety level 3 plus laboratory. This must be coordinated in conjunction with state and local health departments and, when highly suspected, the Centers for Disease Control and Prevention (CDC).

D. Treatment.

1. Institute droplet precautions: In suspected avian influenza (H5N1 or H7N9) infection, place the patients in airborne precautions in a negative-pressure room.
2. Oseltamivir 75 mg orally twice daily or zanamivir 10 mg (two inhalations) twice daily for at least 5 days of therapy. Both agents can reduce duration of symptoms, although oseltamivir resistance has been reported in H5N1 strains.
3. Start empiric antibiotic therapy if secondary bacterial pneumonia is suspected.

II. HANTAVIRUS CARDIOPULMONARY SYNDROME

A. General principles.

1. Hantavirus cardiopulmonary syndrome (HCPS) is an acute febrile illness, characterized by bilateral diffuse interstitial edema that may radiographically resemble the ARDS, with respiratory compromise requiring supplemental oxygen, often developing within 72 hours of hospitalization.

B. Pathogenesis.

1. The illness is caused by rodent-borne viruses within the genus *Hantaviridae*.
2. Aerosols of virus-contaminated rodent urine or perhaps feces represent the main vehicle for transmission. Infection results in a marked increase in pulmonary vascular permeability leading to shock and acute lung injury.

C. Diagnosis.

1. Clinical manifestation and epidemiologic features.
2. Common laboratory abnormalities include simultaneous appearance of thrombocytopenia, leukocytosis with left shift, and presence of immunoblasts in peripheral smear.
3. Serologic studies.
4. Detection of the virus from peripheral blood or serum.
5. Molecular techniques (e.g., PCR assay).

D. Treatment.

1. Adequate cardiopulmonary support. Patients with severely compromised cardiac output should be considered for extracorporeal membrane oxygenation (ECMO) and should be referred to ECMO center.

2. Early use of vasopressors and cautious use of intravenous fluids due to associated capillary leak syndrome.
3. Ribavirin use in an early stage of the illness may be beneficial but is of uncertain benefit.

III. SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

A. General principles.

1. Rapidly progressive respiratory illness caused by coronavirus, called SARS–associated coronavirus (SARS–CoV).
2. SARS–CoV infection was first reported in Asia in 2003 and was associated with a pandemic at that time. Since 2004, no human cases of SARS have been reported anywhere in the world.
3. SARS should be suspected in a patient with fever, cough, or shortness of breath, within 10 days of exposure to one of the following: close contact to a person diagnosed with SARS–CoV infection, a history of travel to an area with recent local transmission of SARS, and employed in an occupation at particular risk for SARS–CoV infection. Also consider SARS as the etiologic agent for a cluster of cases of atypical pneumonia without alternative diagnosis.

B. Pathogenesis.

Knowledge of the pathogenesis is limited. Mannose-binding lectin deficiency may lead to increase susceptibility to infection.

C. Diagnosis.

1. Clinical manifestation and epidemiologic features.
2. Serologic studies.
3. Detection of the virus by a positive reverse transcriptase polymerase chain reaction (PCR) from at least two sites, such as the respiratory tract, stool, serum or plasma or from the same site at two different times, or repeat positive PCR on the same sample.
4. Routine laboratory studies are nondiagnostic.

D. Treatment.

1. Isolate patient in a negative pressure room.
2. No specific treatment recommended except for supportive care.

IV. MIDDLE EAST RESPIRATORY SYNDROME (MERS)

A. General principles.

1. Respiratory illness, typically rapidly progressing, caused by MERS–associated coronavirus (MERS–CoV), a novel coronavirus closely related to bat coronaviruses.
2. Since April 2012, 90 virologically confirmed human infections with MERS–CoV have been reported from several countries in the Middle East as well as Europe. The majority of cases have occurred in Saudi Arabia.

3. The disease is suspected in a patient with acute respiratory infection, who has a fever, cough, or shortness of breath and history of travel to the Arabian Peninsula or neighboring countries within 14 days; or contact with symptomatic traveler who developed fever and acute respiratory illness within 14 days of travel to the Arabian Peninsula or neighboring countries.

B. Diagnosis.

1. Clinical manifestation and epidemiologic feature.
2. A real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) of samples collected from different sites and at different times will increase the likelihood of detecting MERS–CoV. The samples should be preferentially obtained form lower respiratory tract.
3. Serologic testing has limited sensitivity and specificity.

C. Treatment.

1. Isolate patient in negative pressure room.
2. No specific treatment except for supportive care.

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71 Malaria and Other Vector-Borne Illnesses

Iva Zivna and Richard T. Ellison III

I. MALARIA

A. General principles.

1. Malaria is transmitted from person to person by mosquito vectors and rarely by blood transfusion. Malaria caused by *Plasmodium falciparum* is more acute and severe than malaria caused by other *Plasmodium* species.
2. Severe malaria is defined as acute malaria with levels of parasitemia >5% and/or major signs of organ dysfunction.
3. Malaria is endemic in most tropical countries.

B. Pathogenesis.

1. After inoculation, sporozoites invade and replicate in hepatocytes. Infected hepatocytes rupture; merozoites enter the bloodstream and invade erythrocytes, causing fever and leading to the pathologic process of erythrocyte loss and sequestration in the microvascular bed.

C. Diagnosis.

1. Clinical manifestations are fever and rigors; this can progress to altered consciousness with seizures and multiorgan failure.
2. Routine laboratory findings are anemia, hyperbilirubinemia, hypoglycemia, and metabolic acidosis.
3. Definitive diagnosis is made by evidence of parasites on thin and thick smear; rapid diagnostic tests for malaria-specific antigens are now available, as are more expensive PCR assays.

D. Treatment of severe malaria.

1. Artesunate intravenously at dose 2.4 mg/kg at 0, 12, and 24 hours, followed by 2.4 mg/kg once a day for 3 to 5 days. In the USA, the drug is available under investigational protocol from the CDC, Malaria Hotline: (770) 488-7788 and (770) 488-7100.
2. Quinidine gluconate intravenously at loading dose 10 mg salt /kg over 1 to 2 hours (maximum 600 mg salt) followed by 0.02 mg salt/kg/min by continuous infusion. This agent must be administered in an intensive care setting. Criteria for switch to oral regimen are ability to tolerate PO and level of parasitemia <1%. Duration of treatment will vary depending on where the parasite was acquired.
3. Treatment with quinidine should be combined with doxycycline, tetracycline, or clindamycin.

II. WEST NILE VIRUS

A. General principles.

1. West Nile virus (WNV) is a mosquito-borne disease caused by an RNA virus, genus *Flaviviridae*.
2. WNV is one of the most widely distributed arboviruses, affecting North America as well as parts of Europe, the Middle East, Asia, and Africa.

B. Pathogenesis.

1. After inoculation, the virus replicates, leading to viremia that seeds various organs and tissues.

C. Diagnosis.

1. Clinical manifestations can range from asymptomatic to neuroinvasive disease, which can present as encephalitis, meningitis, or flaccid paralysis.
2. Routine laboratory findings are nonspecific. In patients with neuroinvasive disease, the cerebrospinal fluid (CSF) usually demonstrates pleocytosis with predominance of lymphocytes and an elevated protein concentration.
3. Serologic studies in serum or CSF, or nucleic acid testing (NAT) confirms the diagnosis.

D. Treatment.

Supportive treatment.

III. TULAREMIA

A. General principles.

1. Tularemia is a potentially lethal zoonotic infection caused by a gram-negative bacterium, *Francisella tularensis*. Transmission to humans occurs from contact with contaminated animals or a biting insect. Transmission can also occur from airborne spread of contaminated materials.
2. Tularemia affects North America, most of the European countries, the Middle East, and part of Asia.

B. Pathogenesis.

1. After multiplying at the site of inoculation, the organism spreads systemically via a lymphohematogenous route causing an inflammatory reaction and leading to tissue necrosis.

C. Diagnosis.

1. Clinical manifestations of rapid onset of fever and malaise; additional signs and symptoms depend on the portal of entry. Pneumonic tularemia results from direct inhalation of the organism into the lungs; typhoidal tularemia may result from any portal of entry. The ulceroglandular form of tularemia arising at the site of cutaneous inoculation is the most common form of tularemia.
2. Laboratory findings include thrombocytopenia, elevated liver enzymes, and hyponatremia but are often nonspecific.

3. Serologic testing is supportive of the diagnosis. A fourfold or greater rise in titer between acute and convalescent sample is usually needed for diagnostic confirmation. Cultures should be inoculated on supplemented media to confirm the diagnosis. Laboratory personal should be notified, as culture of the organism represents a potential danger.

D. Treatment.

Streptomycin at dose 7.5 to 10 mg/kg intramuscularly every 12 hours for 7 to 14 days or gentamicin intravenously at dose 3 to 5 mg/kg in divided doses for 7 to 14 days. Addition of doxycycline or chloramphenicol to aminoglycoside is required for treatment of tularemic meningitis.

IV. ROCKY MOUNTAIN SPOTTED FEVER

A. General principles.

1. Rocky Mountain spotted fever (RMSF) is a potentially lethal tick-borne disease caused by the intracellular parasite *Rickettsia rickettsii*.
2. RMSF is widespread in the United States. The prevalence of the disease is higher in the South Atlantic states and Central regions than in the Rocky Mountain states. The highly endemic areas include North Carolina and regions of Oklahoma and Arkansas.

B. Pathogenesis.

1. After inoculation and intracellular proliferation, the organism attaches to vascular endothelium causing vasculitis, hemorrhage, edema, and eventually shock.

C. Diagnosis.

1. Clinical manifestations of high fever, severe headache, and maculopapular rash develop 3 to 5 days after fever onset and may involve palms and soles. Suspect in the presence of risk factors and epidemiologic features. Rash is absent in up to 10% of patients.
2. Laboratory findings are thrombocytopenia, hyponatremia, and elevated serum transaminases, but often are nonspecific.
3. Evidence of *R. rickettsii* on a skin biopsy; molecular techniques (e.g., polymerase chain reaction [PCR] assay) or a fourfold rise in specific antibody titers confirms the diagnosis.

D. Treatment.

1. Doxycycline 100 mg orally or intravenously twice a day or chloramphenicol (50 to 75 mg/kg/d) usually administered for 7 days.

V. BABESIOSIS

A. General principles.

1. Babesiosis is a tick-borne disease seen predominantly on the Northeast coast of the United States. Rarely infection can arise through blood transfusion.
2. In the United States, babesiosis is caused by the protozoan, *Babesia microti*, which infects red blood cells and produces mild to severe hemolytic anemia.

3. Can occur concurrently in patients coinfected with the organisms that cause Lyme disease, ehrlichiosis, or anaplasmosis (prevalence of coinfection approximately 25%).

B. Pathogenesis.

1. After inoculation, the organism multiplies inside erythrocytes causing hemolysis. The disease is more commonly recognized and more severe in asplenic individuals.

C. Diagnosis.

1. Clinical manifestations can range from asymptomatic infection to severe hemolytic anemia with multisystem organ failure.
2. Laboratory findings may include anemia, thrombocytopenia, and unconjugated hyperbilirubinemia.
3. Definitive diagnosis is made by evidence of intraerythrocytic parasites on thick and thin peripheral blood smear, serologic studies, or molecular techniques (e.g., PCR assay).

D. Treatment.

1. Combination antibiotic therapy.
   a. Azithromycin intravenously or orally at dose 500 mg once followed by 250 mg daily thereafter and atovaquone 750 mg orally twice a day or
   b. Quinine orally 650 mg every 6 to 8 hours and clindamycin 300 to 600 mg intravenously or intramuscularly every 6 hours for 7 to 10 days.
2. In severe cases transfusion exchange therapy can be effective.

VI. EHRLICHIOSIS AND ANAPLASMOSIS

A. General principles.

1. These are very similar tick-borne diseases caused by the intracellular pathogens *Ehrlichia chaffeensis* (human monocytic ehrlichiosis) and *Anaplasma phagocytophilum* (human granulocytic anaplasmosis).
2. Ehrlichiosis is endemic in the southern part of the United States, especially Arkansas, whereas anaplasmosis is found mainly along the Northeast coast of the United States.
   a. *Anaplasma phagocytophilum* may be transmitted by *Ixodes scapularis*, the tick that is also the vector of Lyme disease and babesiosis.

B. Pathogenesis.

1. *Ehrlichia chaffeensis* primarily infects mononuclear leukocytes and forms inclusion bodies "morulae" in the cytoplasm; *A. phagocytophilum* infects granulocytes.

C. Diagnosis.

1. Clinical manifestations of high fever, severe headache, malaise, and myalgia in association with appropriate risk factors and epidemiologic features.

2. Laboratory studies may reveal leukopenia, thrombocytopenia, and elevated serum transaminase levels.
3. Presence of intraleukocytic morulae, serologic studies, or molecular techniques (e.g., PCR assay) confirms the diagnosis.

D. Treatment.

1. Doxycycline orally or intravenously at dose 100 mg twice daily or chloramphenicol usually administered for 10 days.

VII. LYME DISEASE

A. General principles.

1. A tick-borne illness caused by pathogenic species of the spirochete *Borrelia burgdorferi sensu lato* in North America, *Borrelia afzelii* or *garinii* in Europe and Asia.
2. Lyme disease is the most common tick-borne infection in the United States and Europe, it also occurs in Russia, Japan, and China.
3. Lyme disease can present as early localized, early disseminated, and late disease. Lyme carditis is the most frequently seen presentation of Lyme disease in critical care settings. Lyme carditis is associated with varying severity of atrioventricular (AV) conduction block. In Europe, *B. garinii* or *B. afzelii* may rarely cause chronic encephalomyelitis.
4. Anaplasmosis, ehrlichiosis, and babesiosis can be simultaneously present due to co-infection.

B. Pathogenesis.

After inoculation into the skin, *Borrelia* sp. begins to multiply rapidly. Dissemination to distant sites begins within 2 to 3 days. Innate immune effector cells such as neutrophils and macrophages and recruitment of T cells and B cells to the site of infection play role in host response.

C. Diagnosis.

1. Clinical manifestation can range from mild disease to disseminated Lyme disease with acute cardiac or neurologic involvement.
2. Microbiologic cultures in general are only available in research settings and are infrequently positive.
3. Molecular assays for *B. burgdorferi* DNA can be positive in synovial fluid before treatment, but have poor sensitivity in the CSF.
4. Serologic testing.

D. Treatment of severe Lyme carditis or severe neurologic disease.

1. Lyme carditis.
   a. Ceftriaxone 2 g intravenously daily until high-grade AV block has resolved and the PR interval is less than 300 milliseconds. The patient may then be switched to oral therapy with doxycycline or amoxicillin or cefuroxim to complete 21 to 28 days of treatment.
   b. Temporary pacemaker may be needed in patients with severe and/or symptomatic AV block.
2. Lyme meningitis or encephalomyelitis.

Ceftriaxone 2 g intravenously daily for 10 to 28 days.

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SECTION 7

Gastrointestinal and Hepatobiliary Problems in the Intensive Care Unit

Dominic J. Nompleggi

72 Gastrointestinal Bleeding: Principles of Diagnosis and Management

Darrell M. Gray II and C. Prakash Gyawali

I. GENERAL PRINCIPLES

Acute gastrointestinal bleeding (GIB) is a common clinical emergency that leads to >300,000 hospitalizations annually.

A. Definitions: Upper GIB refers to blood loss proximal to the ligament of Treitz, whereas lower GIB describes bleeding distal to the ligament of Treitz.

B. The clinical history and physical exam are critical components of early risk stratification and may give insight into the etiology and site of bleeding. Rapid triage of high-risk patients allows for urgent intervention and prevention of mortality.

II. ETIOLOGY

A. Upper GIB.

1. Common causes.

a. Peptic ulcer disease.

i. This includes duodenal and gastric ulcers and erosions. Peptic ulcer disease constitutes the most common cause of upper GIB.
ii. Helicobacter pylori infection and nonsteroidal anti-inflammatory drug (NSAID) use are typical causes.

b. Varices.
i. This includes esophageal, gastric, and less frequently, duodenal varices.
ii. Typically seen with cirrhosis and portal hypertension.
iii. Isolated gastric varices can occur with splenic vein thrombosis.

c. Other esophageal causes include esophagitis and Mallory-Weiss tears.
i. Esophagitis is rarely associated with severe bleeding.
ii. Mallory-Weiss tears may be associated with vomiting and retching.

2. Uncommon causes.
a. Vascular ectasias.
i. Angiodysplasia, telangiectasia, Dieulafoy lesions, and gastric antral vascular ectasia are typical vascular ectasias seen in the foregut.
ii. Angiodysplasia can be associated with renal failure and congestive heart failure.
iii. Telangiectasia can be seen in the lips, tongue, nasopharynx, stomach, and small bowel in hereditary hemorrhagic telangiectasia (HHT).

b. Tumors, both benign (e.g., gastrointestinal stromal tumor) and malignant (e.g., adenocarcinoma, lymphoma), can be associated with GIB.

c. Other causes include portal gastropathy, Cameron lesions, aortoenteric fistula, foreign body ingestion, hemobilia, and hemosuccus pancreaticus.

B. Lower GIB.

1. Common causes.
a. Diverticulosis constitutes the most common cause of lower GIB.
b. Anorectal disease, including hemorrhoids and anal fissures.
c. Colitis including inflammatory bowel disease, infectious colitis, ischemic colitis.
d. Angiodysplasia.
e. Tumors and polyps, including postpolypectomy bleeding.

2. Uncommon causes.
a. Rectal ulcers including stercoral ulcers and solitary rectal ulcer syndrome.
b. Radiation proctopathy and colopathy.
c. Vasculitis.
d. Meckel diverticulum.
e. Colonic varices.
f. Other causes, including endometriosis, intussusception, aortoenteric fistula.

III. DIAGNOSIS

A. Clinical presentation.

1. Hematemesis consists of vomiting of either fresh blood or altered blood (coffee-ground emesis). This is indicative of acute upper GIB.
2. Hematochezia consists of passage of bright or dark red blood through the anus.
   a. This is most commonly a manifestation of lower GIB.
   b. Brisk upper GIB can manifest as hematochezia, when it is almost invariably associated with hemodynamic instability.
3. Melena consists of passage of black, sticky, tarry stools.
   a. Frequently the result of an upper GIB, but can be seen in slow lower GIB.
   b. Melena can persist for several days after GIB has ceased, and the stool may remain positive for occult blood for up to 2 weeks.

B. Diagnostic tests.

1. Nasogastric aspiration and lavage can be helpful in risk stratification when acute upper GIB is suspected.
   a. Aspiration of red blood should prompt urgent endoscopy for further investigation and/or treatment.
   b. Lavage may help remove clots from the stomach in preparation for endoscopy and provide an indication of the acuity and rapidity of bleeding.
   c. The nasogastric aspirate may be nonbloody if a tightly closed pylorus prevents reflux of blood from a duodenal bleeding site.
2. Conventional endoscopy.
   a. Endoscopy is ideally performed when the patient is hemodynamically stable.
   b. Esophagogastroduodenoscopy (EGD) is the diagnostic procedure of choice for evaluating and treating an upper GI source of bleeding.
      i. EGD should be performed within 24 hours of presentation in patients with evidence of acute blood loss of suspected upper GI origin.
   c. Colonoscopy is the most frequently performed procedure in detecting and treating the source of a lower GIB.
      i. This is preferably performed after adequate resuscitation and bowel cleansing as the presence of stool and blood in the colonic lumen can obscure visualization and prevent treatment of a culprit lesion.
   d. Push enteroscopy evaluates the proximal small bowel when a bleeding site is not found in the upper GI tract or colon on EGD or colonoscopy.
3. Capsule and advanced endoscopic procedures.
   a. Capsule endoscopy is generally performed when a small bowel source of GIB is suspected or GIB cannot be localized by conventional endoscopic techniques. The procedure is not therapeutic, and real-time interpretation is not typically available.
   b. In selected centers, single-balloon, double-balloon, and spiral enteroscopy are offered as diagnostic and therapeutic modalities in GIB distal to the ligament of Treitz.

4. Imaging studies.
   a. A ^{99m}technetium (^{99m}Tc)-labeled red blood cell scan can detect bleeding rates as low as 0.1 mL/minute under experimental conditions.
      i. This is a reasonable initial imaging test in patients with evidence of active and rapid lower GIB and is often used as a screening tool before a therapeutic angiography.
   b. Angiography requires bleeding rates of 0.5 to 1 mL/minute for identification of a bleeding site.
      i. If a source of bleeding is detected, embolization or infusion of vasopressin can be therapeutic.
   c. Arterial phase multidetector row computed tomography (CT). Sensitivity of this imaging examination is comparable to radiolabeled red blood cell scans. Choice of investigative modality depends on availability of technique and local expertise.

IV. TREATMENT

A. Initial approach.

1. Rapid triage and assessment: A qualitative and quantitative assessment of the degree of blood loss is useful, as the initial blood count may not reflect the degree of blood loss.
   a. Clinical history and physical exam.
      i. Mental confusion, agitation, diaphoresis, mottled skin (livedo reticularis), and cold extremities accompany hypotension with hemorrhagic shock and indicate profound blood loss.
      ii. Abdominal pain is not common with GIB and may indicate the presence of hemobilia, intestinal infarction, or perforation.
      iii. Chest pain may imply a superimposed myocardial infarction or other cardiovascular consequence from anemia and hypotension.
      iv. Previous abdominal vascular graft surgery is a risk factor for bleeding from an aortoenteric fistula.
   b. Initial blood testing should be performed for baseline blood count, coagulation parameters, and complete metabolic profile and to type and cross-match blood for transfusion.
2. Resuscitation.
   a. Resuscitation of the unstable patient takes precedence over other treatments.
   b. Recognizing and aggressively treating intravascular volume depletion is of the highest priority and should proceed concurrently with the initial diagnostic evaluation.
   c. Intravenous access with large-bore peripheral catheters or a central venous catheter is needed for aggressive administration of fluids or blood products.
   d. Massive hematemesis may require endotracheal intubation for airway protection before endoscopy.
   e. Exsanguinating hemorrhage may require immediate surgical management, at times with assistance of limited endoscopy to help direct the surgical approach.

3. Pharmacologic therapy in upper GIB.
   a. Nonvariceal bleeding.
      i. Acid suppression: Early treatment with intravenous proton pump inhibitors is standard in acute upper GIB.
      ii. Prokinetics: IV erythromycin or metoclopramide hastens emptying of blood from the stomach and reduces the need for repeat EGD in patients with acute bleeding.
   b. Variceal bleeding.
      i. Octreotide (usually administered as 25 to 100 μg IV bolus followed by a continuous infusion at 25 to 50 μg/hour for 48 to 120 hours) and antibiotics (IV ceftriaxone or ciprofloxacin) should be initiated early if a variceal bleed is suspected.

B. Endoscopy.

1. Endoscopic therapy, using thermal devices (heater probe, electrocoagulation, laser), hemoclips, injection therapy (sclerosing solutions, hypertonic saline, epinephrine), or banding devices, offers a convenient and expedient method of treating upper GIB from many causes.
   a. These treatments can decrease further bleeding, shorten hospital stay, decrease transfusions, decrease emergency surgery, and lower costs.
2. Recurrent bleeding occurs in up to 30% of patients with bleeding ulcers despite successful endoscopic therapy, and continued observation for up to 72 hours is recommended.

C. Angiographic therapy.

1. Intra-arterial vasopressin has been used for angiographic management of upper and lower GIB. There is a risk of cardiovascular complications.
2. Gelfoam or metal coil embolization of the bleeding artery is an alternate approach, which causes localized thrombosis and vessel occlusion; tissue ischemia and perforation are potential complications.
3. In the upper GI tract, angiographic therapy is usually reserved for bleeding peptic ulcer disease when endotherapy has failed or in patients with a prohibitive surgical risk.

D. Nonsurgical management in variceal bleeding.

1. Transjugular intrahepatic portosystemic shunt (TIPS): This is indicated in patients with variceal bleeding refractory to endoscopic management and in those who have had multiple episodes of variceal bleeding.
2. Balloon tamponade: This is typically used as a temporizing measure when an alternate therapeutic procedure (e.g., repeat endoscopy, TIPS) is planned within 24 hours.

E. Surgery.

1. Surgical consultation should be obtained early in patients with clinical and endoscopic risk factors for high morbidity and mortality.
2. Patients with massive ongoing hemorrhage that overwhelms the resuscitative effort need urgent surgical assessment.
3. Patients failing to respond to endoscopic or angiographic management also need surgical assessment.

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73 Stress Ulcer Syndrome

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I. GENERAL PRINCIPLES

A. Definition.

1. The term stress ulcer refers to mucosal damage in the upper gastrointestinal (GI) tract that occurs with extreme physiologic stress.
2. When associated with clinical bleeding or perforation, the condition is called stress ulcer syndrome (SUS).

B. Description.

1. Stress ulcers occur predominantly in the fundus and body of the stomach.
2. Duodenal ulcers are uncommon in SUS, but when seen, are usually in conjunction with proximal gastric lesions.
3. Bleeding from SUS typically occurs within 2 weeks of intensive care unit (ICU) admission and usually presents as hematemesis, gross blood from a nasogastric tube, or melena.

C. Epidemiology.

1. As many as 52% to 100% of patients admitted to ICUs have endoscopic evidence of gastric mucosal damage within the first day of ICU admission, but most are asymptomatic.
2. Overt GI bleeding is estimated to occur in 1.5% to 8% of ICU patients.

D. Prognosis.

1. Mortality rates can be as high as 50% to 80% in patients who bleed, although death is usually attributed to the underlying disease.
2. Stress ulcer bleeding may serve as a marker for severely ill patients.

II. ETIOLOGY

A. Patients in ICU with coagulopathy or requiring mechanical ventilation for >48 hours are statistically more likely to develop SUS.

B. Shock, hypotension, sepsis, and major burns (>35% body surface area) are more common in patients with SUS.

C. Patients with acute intracranial head trauma and coma (Curling and Cushing ulcers, respectively) are also at increased risk of having stress ulcers.

III. PATHOGENESIS

A. Mucosal damage.

1. Although gastric acid is essential for stress ulceration, the following impairments of mucosal defense mechanisms are also required:
   a. Disruption of the bicarbonate-rich mucus layer lining the stomach by refluxed upper intestinal contents including bile salts.
   b. Failure of mucosal cell reorganization, which normally helps to cover denuded mucosa.
2. Stress results in splanchnic vasoconstriction leading to gastric mucosal ischemia, which ultimately leads to both a decrease in synthesis of mucus, and a drop in intramucosal pH from a deficit of systemic bicarbonate that normally buffers back diffusion of hydrogen ions.
3. Subsequent reperfusion contributes to injury from hyperemia and an enhanced inflammatory response while decreasing the synthesis of cytoprotective prostaglandins.

IV. DIAGNOSIS

A. Clinical presentation.

1. Stress ulcers come to clinical attention when they bleed.
2. Significant stress ulcer bleeding occurs in 2% to 6% of critically ill patients and presents within 14 days of the onset of physiologic stress or ICU admission as hematemesis, gross blood from the nasogastric tube, or melena.
3. Patients with thermal injury from burns or with an acute intracranial disease, including head trauma and coma, appear to be at increased risk (Curling ulcers and Cushing ulcers).
4. Abdominal pain is unusual except in the infrequent setting of perforation.

B. Endoscopy.

1. The earliest mucosal changes are found in the most proximal part of the stomach and include pallor, mottling, and submucosal petechiae.
2. Superficial linear erosions and ulcers are formed when these lesions coalesce.
3. Eventually, diffuse mucosal damage may result, with bleeding and rarely, perforation.

V. TREATMENT

A. Principles.

1. The risk of bleeding and overall prognosis are related to the severity of the underlying illness, aggressive management of which should always take precedence. Maintaining adequate hemodynamic support is key in prevention of SUS.

B. Prophylaxis.

1. Antisecretory drugs.

a. Histamine-2-receptor antagonists.
   i. Administered by intermittent intravenous (IV) bolus or, preferably, continuous infusion, which is better at maintaining the desired gastric pH levels.
   ii. Patients with a creatinine clearance of <30 mL/minute should receive half the recommended dose, and caution should be exercised in patients with thrombocytopenia.
   iii. Reduces the incidence of clinically important bleeding without increasing the risk for ventilator-associated pneumonia.
   iv. Effectiveness of raising pH may be limited by a tolerance that develops to the drug.
b. Proton pump inhibitors (PPIs).
   i. These are the strongest antisecretory agents.
   ii. Can be administered enterally or intravenously at once-a-day dosing.
   iii. The need for aggressive acid suppression with a PPI is not established for stress ulcer prophylaxis, although recent studies have shown that PPIs prevent GI bleeding more effectively than H2 blockers.

2. Antacids.
   a. Antacids (10 to 80 mL) can be administered through a nasogastric tube every 1 to 2 hours and ideally titrated to keep the gastric pH > 4.0, measured 1 hour after administration.
   b. Some antacids may cause diarrhea, may be contraindicated in renal failure, and may affect the bioavailability of oral medications.
   c. Antacid use involves expensive and time-consuming processes of frequent administration and monitoring of gastric pH.
3. Sucralfate.
   a. Sucralfate coats the early shallow mucosal lesions and protects them from further acid and pepsin damage without altering gastric pH.
   b. It is delivered in the form of a slurry through a nasogastric tube at a dose of 4 to 6 g/day.
   c. Although it is safe for long-term use in critically ill patients, sucralfate should be used with caution in patients with chronic renal insufficiency.
   d. Sucralfate may have a lower incidence of nosocomial pneumonia. It has a low side effect profile and is inexpensive.
4. Other agents.
   a. Prostaglandins, free radical scavengers such as dimethylsulfoxide and allopurinol, and the bioflavin meciadanol have also been used for stress ulcer prophylaxis with varying results.

C. GI bleeding.

1. Upper GI endoscopy helps establish the diagnosis and can provide local control of bleeding with endoscopic therapy such as injections of epinephrine, hemoclipping, and/or thermal therapy.
2. If endoscopic measures fail, angiography can be attempted, using intra-arterial vasopressin or embolization if the bleeding site can be demonstrated.

3. Surgical therapy is reserved for severe, life-threatening hemorrhage unresponsive to all other measures.
4. Total gastrectomy may be better at controlling bleeding compared to subtotal gastrectomy, but it has a very high mortality rate in critically ill patients.
5. Vagotomy and oversewing of any remaining ulcers during subtotal gastrectomy may decrease the high rate of recurrent bleeding.

VI. COMPLICATIONS

A. Complications of stress ulcers.

1. Stress ulcers can develop bleeding, and rarely, perforation.

B. Complications of prophylaxis.

1. Nosocomial pneumonia as a complication of stress ulcer prophylaxis is a growing concern.
   a. Gastric alkalinization and increased colonization of the upper GI tract with potentially pathogenic organisms are thought to play a causal role.
   b. Consequently, some studies suggest a higher incidence of nosocomial pneumonia in patients who receive antisecretory drugs.
   c. Further studies are needed before one prophylactic agent confidently can be recommended over another because of either higher efficacy or lower complications from treatment.
2. *Clostridium difficile* infection.
   a. Gastric acid plays an important role in protection against *C. difficile* infection, and some studies suggest that the use of acid-suppressive therapy can lead to increased rates of *C. difficile* infection.

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74 Variceal Bleeding

Susan Hongha T. Vu and C. Prakash Gyawali

I. GENERAL PRINCIPLES

A. Variceal bleeding is the most common lethal complication of cirrhosis.

B. The mortality of an acute bleeding episode is 20% at 6 weeks. The mortality approaches 40% at 2 years without liver transplantation.

C. Varices are present in 50% of patients with cirrhosis. This proportion increases with severity of liver disease, with 85% of Child-Pugh class C cirrhotics manifesting varices.

D. Spontaneous bleeding occurs at a rate of 5% to 15% per year.

E. While exsanguination remains the most immediate threat to life, mortality is often related to liver decompensation, aspiration, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, septicemia, or alcohol withdrawal.

F. Survival is dependent on maintaining a high index of suspicion, aggressive resuscitation and stabilization of hemodynamics, early endoscopy for diagnosis and treatment, and prevention of superimposed complications and recurrent bleeding.

II. PATHOPHYSIOLOGY

A. Portal hypertension.

1. Portal hypertension is caused by intrahepatic resistance to portal venous flow from the hepatic fibrosis and architectural distortion that is seen in cirrhosis.
   a. Other causes include portal vein and hepatic vein thrombosis, congenital hepatic fibrosis, and schistosomiasis.
2. Secondary hemodynamic changes associated with cirrhosis may contribute to increased portal pressure, including intrahepatic vasoconstriction and splanchnic arteriolar vasodilatation, decreased systemic vascular resistance, and increased cardiac output.

B. Development of varices.

1. Portosystemic collateral circulation develops to decompress the portal venous system. The most clinically significant locations where collaterals develop are the junctions of squamous and columnar mucosae (gastroesophageal, anal, and peristomal). These collateral vessels progressively enlarge to form varices when the portosystemic pressure gradient exceeds 10 mm Hg.
   a. Esophageal varices are graded based on size, with large ones measuring ≥5 mm.

b. Gastric varices are classified as GOV (extension of esophageal varices) or IGV (isolated gastric varices in the absence of esophageal varices). GOV are treated similarly to esophageal varices, whereas there are limited data on managing IGV.

2. Risk factors for variceal rupture include large size, portosystemic pressure gradient ≥12 mm Hg, red wale marks, decompensated cirrhosis, and active infection.

III. DIAGNOSIS

A. Clinical presentation.

1. Variceal bleeding presents as hematemesis, melena, or hematochezia when brisk, and is often accompanied by varying degrees of hemodynamic instability.

2. Acute bleeding is self-limited in 40% to 50% of cases; however, these may represent sentinel bleeds that may precede massive bleeding with high rebleeding rates.

3. Nonvariceal sources of hemorrhage account for 10% to 50% of upper gastrointestinal bleeding in cirrhotics, so endoscopic verification is recommended.

B. Endoscopy.

1. The gold standard of diagnosing variceal bleeding is upper endoscopy.

2. Endoscopic findings supporting variceal bleeding include active bleeding, a fresh fibrin clot protruding from a varix, a nipple-like protrusion from a varix, red wale marks, or large varices with no other potential bleeding source.

3. Nonbleeding varices are more commonly found than bleeding varices on endoscopy; in such instances, in the absence of an alternate bleeding source, variceal band ligation is warranted because of the high rate of early recurrent bleeding.

IV. TREATMENT

A. Initial resuscitation.

1. Appropriate resuscitative efforts should be initiated without delay and before endoscopic evaluation. Endotracheal intubation may be required for airway protection, especially in the massively bleeding or obtunded patient. The patient should be hemodynamically stabilized with fluid resuscitation, transfusion, and vasopressors if needed.

2. Packed red blood cell transfusion, fresh frozen plasma, and platelet infusion may be necessary before endoscopy, depending on initial laboratory test results. When massive transfusions are necessary, the patient should be monitored for resultant hypocalcemia and thrombocytopenia.

3. Nasogastric aspiration may be necessary when the diagnosis of an upper gastrointestinal hemorrhage is in doubt; fears of trauma to a varix from the tube largely are unfounded, but good lubrication and careful technique should be exercised. Nasogastric aspiration also aids in clearing the stomach and esophagus of blood before upper endoscopy for better visualization.

B. Pharmacotherapeutic agents.

1. Octreotide is the pharmacotherapeutic vasoconstrictor of choice in acute variceal bleeding. It is a long-acting analog of somatostatin that inhibits the release of vasodilators, thus reducing splanchnic blood flow and portal pressure.
   a. Octreotide should be initiated immediately when variceal bleeding is suspected. A bolus of 50 μg is followed by a continuous infusion of 50 μg/hour for 3 to 5 days.
   b. Octreotide is effective in stopping active bleeding from varices and has an important role in the prevention of early recurrent bleeding after initial hemostasis.
   c. Transient nausea and abdominal pain may occur, but significant adverse effects are rare.
   d. Somatostatin is not available in the United States, but, when available, should be given as 250-μg bolus followed by 250-μg/hour infusion.
2. Vasopressin, when infused intravenously, is a potent vasoconstrictor that reduces splanchnic blood flow and portal pressure. It is currently used only when octreotide is not available.
   a. The use of vasopressin is limited by adverse cardiac effects (including myocardial ischemia, arrhythmias, hypertension, and peripheral and bowel ischemia), which interfere with treatment in approximately 30% of patients.
   b. The starting dose is 0.2 to 0.4 units/minute, titrated to a maximum of 0.8 units/minute for a maximum of 24 hours to minimize the side effects.
   c. Concurrent intravenous nitroglycerin infusion, starting at 40 μg/minute and titrated to maintain a systolic blood pressure of 90 mm Hg, has been shown to reduce the systemic side effects of vasopressin.
   d. Terlipressin, a synthetic analog of vasopressin with slower release, is not available in the United States, but has fewer side effects. It is administered at a dose of 2 mg every 4 hours and can be titrated down.

C. Endoscopic therapy.

1. Band ligation is the technique of choice for endoscopic control of bleeding varices. It is effective at controlling bleeding in 80% to 90% of cases.
   a. Small elastic rings are placed endoscopically over the varices. Subsequent strangulation of the vessel with sloughing and fibrosis of the adjacent esophageal tissues results in the obliteration of the varix, decompressing downstream veins.
   b. Active bleeding is controlled in 80% to 90% of patients after one or two treatments.
2. Sclerotherapy is performed by injecting a sclerosant solution into the variceal lumen or into the adjacent submucosa to accomplish vascular obliteration. This has similar rates of efficacy as band ligation but with higher rates of complications.

a. Sclerotherapy is reserved for bleeding refractory to band ligation, gastric variceal bleeding, or massive bleeding where there is inadequate visualization of the variceal columns to perform band ligation.

b. Frequently used sclerosants include sodium tetradecyl sulfate, ethanolamine oleate, ethanol, sodium morrhuate, hypertonic dextrose, and phenol.

3. Variceal obturation through injection of tissue adhesives (cyanoacrylate) and thrombin may be used in acute bleeding from gastric varices. However, availability of adhesives and endoscopist experience with this technique may be limited.

a. Complications include rebleeding due to extrusion and distant embolization.

4. Complications of endoscopic therapy include esophageal ulceration, bleeding, stricture formation, dysmotility, perforation, mediastinitis, bacteremia, and aspiration. Band ligation has lower rates of complications compared to sclerotherapy.

D. Balloon tamponade.

1. Gastric and esophageal balloon devices for direct tamponade of the bleeding varices (Sengstaken-Blakemore, Minnesota, and Linton-Nachlas balloons) may be required for patients with severe or persistent bleeding refractory to endoscopic and pharmacologic treatment. Initial success approaches 90%, but recurrent bleeding rates are high.

2. Balloon tamponade serves only as a temporizing measure until definitive therapy can be arranged, which should be performed within 24 to 48 hours of balloon inflation. The esophageal balloon should be inflated to 30 to 45 mm Hg and reduced to 25 mm Hg once bleeding is controlled with periodic checks on pressure and rebleeding.

3. Complications occur in 15% to 30% of patients. These include esophageal/gastric necrosis and perforation, aspiration, and balloon migration.

a. Endotracheal intubation should precede balloon placement for airway protection.

b. Balloon-related deaths occur in up to 6% of patients. Given these potentially lethal complications, balloons should only be inflated for a maximum of 24 hours.

E. Transjugular intrahepatic portosystemic stent (TIPS) shunt.

1. TIPS is a shunt between radicals of the hepatic and portal veins, created by interventional radiologists using ultrasonographic and fluoroscopic guidance to bypass hepatic resistance to blood flow and thus decrease portal pressure. An expandable metal stent is left in place, and the portosystemic pressure gradient is reduced to <12 mm Hg.

a. Cross-sectional imaging or ultrasound with Doppler of the liver is necessary before TIPS placement to evaluate the patency of the portal vessels as well as to rule out liver masses.

2. TIPS is recommended for bleeding refractory to combined pharmacologic and endoscopic therapy, recurrent bleeding, or bleeding from gastric varices or portal hypertensive gastropathy.

3. The technical success rate in constructing a TIPS is >90%, with near-universal success in bleeding control. Recent studies have demonstrated reductions in mortality and treatment failure with early TIPS placement.
   a. Some degree of shunt insufficiency is seen in 15% to 60% of patients within 6 months.
   b. Doppler ultrasound to evaluate shunt patency is recommended for postprocedure bleeding recurrence. The shunt usually can be revised with little morbidity.
4. Twenty percent to thirty percent of patients develop transient deterioration of liver function after elective shunt placement, and up to one-fourth of patients may experience new or worsened hepatic encephalopathy.

F. Balloon-occluded retrograde transvenous obliteration (BRTO).

1. BRTO is an interventional radiologic procedure to manage gastric varices with splenorenal shunts. Left adrenal venography is performed to identify the gastrorenal shunt, which is then occluded with a balloon after which sclerosant is injected proximally to obliterate the gastric varices.
2. BRTO is also used for treatment of small bowel varices via collateral vessels.
3. BRTO may result in increased portal pressure and worsening of other portal hypertensive complications.

G. Other measures.

1. Surgical shunts (i.e., portocaval and distal splenorenal shunts) may be considered in patients with a good long-term prognosis who need portal decompression, such as patients with Pugh Childs class A cirrhosis and patients with noncirrhotic portal hypertension.
   a. The utility of surgical shunting in acute bleeding is limited by high operative mortality. Postprocedure encephalopathy and control of bleeding are similar to TIPS. Altered anatomy may also complicate future liver transplant surgery.
2. Nonshunting operations, such as the Sugiura procedure (mucosal transection and devascularization of the esophagus), are infrequently used because varices reform and bleeding recurs in 20% of patients.
3. Embolization of the short gastric veins in gastric variceal bleeding and splenectomy in splenic vein thrombosis are other potential management options.

H. Prevention of complications.

1. Rebleeding occurs in 60% of untreated patients within 1 to 2 years and is associated with 33% mortality.
   a. Nonselective β-blockers reduce rates of rebleeding to 40%. They decrease portal pressures by reducing cardiac output via β1 and splanchnic vasoconstriction via β2 effects.
      i. β-blockers should not be used in acute variceal bleeding, as they can contribute to hypotension and block the physiologic increase in heart rate. These medications are indicated for secondary prevention of variceal bleeding, and may be initiated once acute

bleeding has resolved and if the patient is hemodynamically stable.

ii. Nadolol 40 mg daily or propranolol 20 mg twice daily is a standard starting dose and should be titrated up as the blood pressure will allow.

b. Serial endoscopic band ligation treatment reduces rebleeding rates to 32%. Scheduled sessions at weekly or biweekly intervals are recommended until obliteration of the varices is achieved.

2. Bacterial infections are found in 20% of cirrhotics with gastrointestinal bleeding. Antibiotic prophylaxis is recommended at onset of bleeding, preferably prior to endoscopy. It has been proven to decrease mortality, infections, and rebleeding.

a. Oral norfloxacin 400 mg twice daily for 5 to 7 days is recommended. Intravenous alternatives include ciprofloxacin 400 mg twice daily or ceftriaxone 1 g daily.

3. Portosystemic encephalopathy may be precipitated by gastrointestinal bleeding, including variceal bleeding. Endoscopy to evaluate for occult bleeding may be considered in patients with encephalopathy when no other trigger is identified. Treatment includes lactulose and rifaximin.

4. Renal failure from acute tubular necrosis or hepatorenal syndrome may occur and may be prevented by early resuscitation.

5. Patients with alcoholism should receive thiamine and be monitored closely for alcohol withdrawal.

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75 Gastrointestinal Motility Problems in the Critical Care Setting

Gregory S. Sayuk

I. GENERAL PRINCIPLES

A. Gastrointestinal (GI) motility abnormalities are common in the intensive care unit (ICU) setting.

B. Motility problems are a consequence of multiorgan dysfunction, medications, and metabolic derangements.

C. As many as two-thirds of ICU patients are affected, predominantly with disordered gastric and colonic motor function.

D. Motility disorders manifest as gastric stasis (producing gastroesophageal reflux disease [GERD]), colonic dysfunction (abdominal distension, constipation), and diarrhea.

E. Typical signs and symptoms often are masked in the unresponsive or sedated patient.

F. GI motility complications prolong ICU stays and are associated with nearly a doubling of mortality risk.

II. ETIOLOGY

A. Critical illnesses.

1. Causes of gastric stasis (delayed gastric emptying, gastroparesis) include the following:
   - **a.** Neurologic (closed head, spinal cord injury).
   - **b.** Inflammatory (infection, sepsis).
   - **c.** Acute pain.
2. Medications resulting in decreased gastric transit.
   - **a.** Anticholinergic medications.
   - **b.** Sympathomimetics/pressor agents.
   - **c.** Narcotics.
   - **d.** Phenothiazines/antipsychotics.
   - **e.** Propofol.
3. Comorbid disorders.
   - **a.** Organ failure (cirrhosis, end-stage kidney disease).
   - **b.** Metabolic diseases (poorly controlled diabetes mellitus, hypothyroidism).
   - **c.** Prior gastric surgery and vagotomy.
   - **d.** Neurologic diseases (Parkinson disease, neuropathy).
   - **e.** Diseases that alter the mucosa (amyloidosis, scleroderma).

4. Metabolic derangements.
   a. Electrolytes (hypercalcemia, hypokalemia, hypomagnesemia).
   b. Hyperglycemia.
   c. Acidosis/alkalosis.
5. Sympathetic neural stimulation often accompanies severe illness, resulting in selective suppression of excitatory motor reflexes and sustained intrinsic inhibitory neural overactivity.
   a. Adverse outcomes from gastric stasis are the following:
      i. Poor absorption of oral- or nasogastric-administered medications.
      ii. Intolerance to enteral feeding.
   b. Predisposition to GERD and its complications (e.g., dysphagia, GI bleeding); GERD is further exacerbated by supine positioning, use of nasogastric tubes, and mechanical ventilation.
      i. Tracheobronchial aspiration and pulmonary compromise.
   c. Causes of colonic dysfunction (distension, constipation) include the following:
      i. Medications, metabolic disturbances, and medical comorbidity (see Section II.A).
      ii. Infection, either systemic (pneumonia, sepsis) or GI (e.g., *Clostridium difficile*, cytomegalovirus).
      iii. Ischemia (intestinal, cerebrovascular).
      iv. Surgical intervention.
      v. Autonomic imbalance accompanying medical and surgical illnesses.
      vi. Supine positioning, as it is not conducive to voluntary elimination.
      vii. The withholding or strict limitation of luminal nutrition, a major stimulant of colonic motor function.
      viii. Combinations of factors, which may precipitate massive colonic dilatation or pseudoobstruction.
   d. Diarrhea complicates as many as 1/3 of episodes of critical care. Its causes, evaluation, and treatment are presented in chapter 79.
6. Enteral feedings.
   a. Of ICU patients receiving enteral nutrition, 40% to 60% develop diarrhea.
   b. Hyperosmolar formulas, higher infusion rates, and colonic fermentation of malabsorbed carbohydrates have been invoked as etiologies.
7. Infections, including *C. difficile*, and in immunocompromised patients, opportunistic pathogens (e.g., cytomegalovirus, herpes simplex virus).
8. Medications (antacids, antibiotics, lactulose, sorbitol-containing medication suspensions).
9. Fecal impaction, with fecal overflow around the impaction.

III. DIAGNOSIS

A. Gastric stasis (delayed gastric emptying, gastroparesis).

1. Gastric stasis is suspected with impaired tolerance to gastric feeding, including clinical evidence of oral regurgitation or tracheobronchial aspiration (e.g., airway suctioning of enteral nutrition products).

2. Gastric residual volumes of 200 mL or greater suggest retention.
3. More reliable measurements of gastric emptying include scintigraphic techniques and octanoate breath testing, but are rarely performed clinically.
4. Mechanical obstruction is evaluated by upper endoscopy or radiographic imaging techniques (abdominal plain films, computed tomography [CT] scan).
5. GERD, as an outcome of gastric stasis, typically presents with heartburn and regurgitation, though critically ill patients may not endorse these symptoms.
   a. Chest pain is an atypical GERD symptom, but mandates exclusion of cardiopulmonary explanations.
   b. GERD should be considered in the setting of unexplained tracheobronchial aspiration, upper GI bleeding, vomiting, or regurgitation.
   c. Endoscopy typically is reserved for evaluation of GERD complications (e.g., GI bleeding) (see Chapter 72).

B. Acute colonic pseudoobstruction (Ogilvie syndrome).

1. Patients typically present with marked abdominal distension, pain, and altered bowel movements.
2. Progression can lead to colonic ischemia and perforation, complications that carry a mortality rate of up to 30%.
3. Colonic distension can be found incidentally on radiographs obtained for other reasons.
4. Plain abdominal films or CT images demonstrate the following:
   a. Diffuse dilatation of the colon with normal mucosal markings and haustra.
   b. Absence of small bowel dilatation.
5. A water-soluble contrast enema or CT may be necessary to exclude mechanical obstruction.
6. CT imaging is the preferred imaging modality in this setting and is the most sensitive test for detecting intestinal perforation.

C. Diarrhea.

Diarrhea (see Chapter 84) is defined by change in stool frequency or consistency, but more objectively by a stool weight of >250 g/day.

1. Diarrhea can result in significant nutrient, water, and electrolyte loss, and, importantly, can contribute to perineal and sacral skin breakdown.
2. Review medications for those who may precipitate diarrhea (see Section II.A.8).
3. Maintain high suspicion for antibiotic-associated diarrhea, especially with unexplained leukocytosis, and diagnose via detection of stool polymerase chain reaction (PCR) for *C. difficile*, which is rapidly replacing the toxin assay because of its superior sensitivity, specificity, and rapid turnover.
4. Perform rectal examination to exclude a distal impaction; abdominal radiographs are required to exclude more proximal impaction.
5. Sigmoidoscopy or colonoscopy with biopsy may be helpful when diarrhea remains unexplained.

IV. TREATMENT

A. Gastric stasis (delayed gastric emptying, gastroparesis).

1. Initial approach.
- **a.** Eliminate iatrogenic factors and exclude mechanical obstruction.
- **b.** Minimize or eliminate narcotics and other provoking medications.
- **c.** Improve feeding tolerance by positioning the feeding tube ports beyond the pylorus (e.g., jejunal or gastrojejunal feeding tube); notably, this maneuver does not eliminate the risk of tracheobronchial aspiration.
- **d.** Prone positioning allows for larger enteral feeding volumes.
- **e.** Parenteral nutrition can be considered if enteral feeds are not tolerated; however, rates of infection and hyperglycemia are greater.

2. Medical/nonpharmacologic treatments.
- **a.** Metoclopramide is the only clinically approved prokinetic in the United States and is the agent of choice in the ICU.
  - **i.** Accelerates gastric emptying, but does not prevent aspiration pneumonia.
  - **ii.** Significant side effects include confusion, agitation, somnolence, and dystonic reactions.
- **b.** Intravenous (IV) erythromycin, a motilin agonist, accelerates gastric emptying and facilitates postpyloric tube placement.
  - **i.** To improve gastric emptying, erythromycin is given at a dose of 1 to 3 mg/kg three to four times daily.
  - **ii.** Side effects include nausea, vomiting, abdominal cramps, and diarrhea.
  - **iii.** Tolerance to the prokinetic effect of erythromycin occurs rapidly with repeated use via motilin receptor down-regulation.
  - **iv.** Erythromycin in combination with metoclopramide may be more effective than either agent alone.

B. Managing GERD as an outcome consequence of gastric stasis.

1. Conservative measures may reduce GERD (e.g., 45-degree elevation to head of bed, avoidance of large-bolus tube feedings, postpyloric feeding tube placement).

2. Pharmacologic treatment also is required.
- **a.** Proton pump inhibitors (PPIs) are the most effective acid-suppressant agents, and may be given by mouth or by nasogastric tube.
- **b.** The IV route of PPI administration may be used when the enteral route is not feasible or absorption is in question; pantoprazole, lansoprazole, and esomeprazole are available parenterally.

C. Acute colonic pseudoobstruction (Ogilvie syndrome).

1. Initial approach.
- **a.** Recognition and correction of potentially reversible precipitants, such as electrolyte imbalances, infection, or medications that slow transit, are essential.
- **b.** Reduce narcotic medication use.
- **c.** Newer μ-opioid receptor antagonists (alvimopan and methylnaltrexone) may be helpful in opioid-induced intestinal dysfunction.

d. Nothing by mouth and implement low, intermittent nasogastric suction.
e. Exclude fecal impaction and place a rectal tube.
f. Follow abdominal examination serially, and pursue abdominal radiographs as dictated by changes in clinical exam.

2. Pharmacologic treatment.
a. The acetylcholinesterase inhibitor neostigmine can be used (2 mg intravenously over 5 minutes) when the patient fails to improve with conservative measures and reversal of underlying factors.
b. Neostigmine is effective in approximately 90% of cases, with a low recurrence rate.
c. Close monitoring is indicated during neostigmine use; it is contraindicated in cases with bradycardia, active bronchospasm, or mechanical bowel obstruction.

3. Colonic decompression.
a. Colonoscopy for decompression is considered when distension worsens or persists, and clinical condition of the patient appears compromised.
b. Overall success of colonoscopic decompression is 88%, though mortality with the procedure in the setting of colonic pseudoobstruction is as high as 2%.
c. The general value of colonoscopic decompression in colonic pseudoobstruction remains controversial; the procedure should be used selectively.

4. Surgical or interventional radiologic decompression occasionally is required when progressive findings of peritoneal irritation are detected on exam, or if imaging indicates perforation.

D. Diarrhea.

1. Initial approach.
a. Decrease feeding rate in tube-fed patients to improve diarrhea until the gut acclimates to the delivery of an increased osmotic and volume load.
b. Recognize and correct electrolyte and other relevant metabolic abnormalities.
c. If possible, discontinue medications potentially responsible for diarrhea, including offending antibiotics in presence of *C. difficile* infection.
d. Incontinence devices (e.g., rectal tube) will minimize skin complications.

2. Pharmacologic treatment.
a. Antidiarrheal agents should be used cautiously in ICU patients; focus first on addressing infectious or other reversible etiologies.
b. Metronidazole remains the drug of choice for *C. difficile* infection.
i. When suspected, initiate therapy in the more severely ill ICU patient while the toxin assay results are pending, and continue treatment for at least 14 days in confirmed cases.
ii. Response of diarrheal symptoms may take as long as 7 to 10 days.

iii. The IV administration route is required in patients intolerant of oral metronidazole.
iv. If broad-spectrum systemic antibiotics cannot be discontinued, maintain metronidazole until their treatment courses are completed.
v. Relapse of *C. difficile* infection is common and typically requires retreatment.

c. Oral vancomycin and fidaxomicin are reserved for patients intolerant of, or who fail to improve with, metronidazole.
d. Adjunct approaches including use of colestipol or cholestyramine as a toxin binder and probiotics may be used; importantly, the sequestrant agents will bind oral vancomycin, and thus must not be administered at the same time.

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76 Fulminant Colitis and Toxic Megacolon

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I. GENERAL PRINCIPLES

A. Definitions.

1. Fulminant colitis.
   a. Fulminant colitis implies a serious progression of colonic mucosal inflammation, extending into the deeper layers of the colon.
   b. Patients typically manifest severe bloody diarrhea, abdominal tenderness, and systemic toxicity.
2. Toxic megacolon.
   a. In the face of fulminant colitis, colonic circular muscle paralysis can precipitate *acute colonic dilatation* or *toxic megacolon*, the term used to describe this entire sequence of events, which includes systemic toxicity.
   b. Toxic megacolon is most commonly seen as a complication of ulcerative colitis or *Clostridium difficile* infection colitis. It can also occur with other inflammatory conditions (Crohn colitis, Behcet disease, and collagenous colitis) and other colonic infections (bacterial: *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Escherichia coli*; parasitic: *Entameba*, *Cryptosporidium*; fungal: Aspergillosis; and viral: Cytomegalovirus [CMV] and rotavirus); ischemia, colonic lymphoma, obstructive colon cancer, volvulus, diverticulitis, Kaposi sarcoma, chemotherapy, and idiopathic colitis are other causes.
   c. Factors associated with increased mortality include age older than 40 years, the presence of colonic perforation, and delay of surgery.
   d. Early recognition and treatment of toxic megacolon can substantially lower mortality from as high as 50% (with colonic perforation) to <15%.
   e. Other conditions that can cause colonic dilation without systemic toxicity include Hirschprung disease, chronic constipation, and intestinal pseudoobstruction.

II. DIAGNOSIS

A. Clinical presentation.

1. History.
   a. Inflammatory colitis.
      i. Toxic megacolon usually occurs in the background of extensive colitis associated with chronic inflammatory bowel disease, especially ulcerative colitis, and, less commonly, Crohn disease.

ii. Toxic megacolon typically occurs during a relapse of established ulcerative colitis; however, 25% to 40% of cases present during an initial attack. Perianal disease and extraintestinal manifestations (joint, eye, skin, and liver) can be clues to a new inflammatory bowel disease diagnosis.

iii. Progressive bloody diarrhea and crampy abdominal pain are typical symptoms. A paradoxical decrease in stool frequency with passage of bloody "membranes" is an ominous sign.

iv. Manipulation of the inflamed bowel with diagnostic examinations such as barium enema or colonoscopy, medications (including vigorous laxatives, antidiarrheals, anticholinergics), electrolyte imbalances, and pH disturbances can contribute to the development of the condition.

v. Corticosteroids can suppress signs of perforation and peritonitis, but whether these drugs can precipitate toxic megacolon is controversial.

b. Infectious colitis.

i. *C. difficile* infections have been the cause of increasing hospitalizations over the last decade, due to increased use of broad-spectrum antibiotics and development of more virulent *C. difficile* strains.

ii. Patients age 65 and older are at increased risk of *C. difficile* infection and a severe course, including toxic megacolon. Other risk factors for megacolon in *C. difficile* colitis are malignancy, chronic obstructive pulmonary disease, renal failure, antiperistaltic medications, and antibiotics, especially clindamycin.

iii. A history of antibiotic use, antidiarrheals, anticholinergics, opiates, health facility contact, or immunosuppression (human immunodeficiency virus [HIV], chemotherapy) should be noted.

iv. Travel to endemic areas may suggest *Entameba* infection.

v. Exposure to others with gastrointestinal infectious symptoms should be elicited.

2. Physical examination.

a. Systemic toxicity is heralded by fever and tachycardia and can progress to hypotension, confusion, agitation, or apathy.

b. Abdominal tenderness and distension, with decreased bowel sounds on auscultation, are common. Constipation and obstipation may be present.

c. Peritoneal signs indicate transmural inflammation or perforation, but they may be minimal or absent in elderly patients or in patients receiving corticosteroids.

B. Diagnostic tests.

1. Laboratory studies.

a. Laboratory tests should assess the degree of systemic toxicity, fluid and electrolyte deficits, pH disturbances, and the need for blood transfusion.

b. Leukocytosis with a significant left shift is common.

c. Elevated C-reactive protein and erythrocyte sedimentation rate is expected.

d. Anemia, hypokalemia, and hypoalbuminemia also commonly occur.
e. Stool should be sent for *C. difficile* polymerase chain reaction (PCR) toxin and other pathogens.
f. In HIV-positive patients, consideration should be given to CMV and *Cryptosporidium*.
g. Blood cultures to assess for bacterial translocation are helpful.
h. Most patients develop hypoalbuminemia.

2. Radiologic studies.
a. Abdominal imaging (plain x-ray, computed tomography) may reveal loss of colonic haustration, segmental or total colonic dilatation (to >6 cm) with mucosal thumbprinting, colonic wall thickening, stranding, air–fluid levels, abscess, intraperitoneal air, ascending pyelophlebitis, or pneumatosis cystoides coli in severe transmural disease.
b. Small bowel ileus may accompany toxic megacolon and is a poor prognostic sign for conservative medical management.
c. Discrepancies may exist between physical and radiographic findings.

3. Endoscopy.
a. A limited proctoscopic examination may show extensive ulceration with friable, bleeding mucosa, or pseudomembranes. Biopsies may be obtained for histology if the etiology of the colitis is uncertain.
b. More extensive endoscopic examination is contraindicated due to the risk of perforation.

4. The most commonly used diagnostic criteria require all components below:
a. A dilated colon on imaging.
b. At least three of the following: fever >38 degrees, tachycardia >120, leucocytosis >10.5 thousand with left shift, and/or anemia.
c. At least one of the following: dehydration, altered mental status, electrolyte abnormalities, and/or low blood pressure.

III. TREATMENT

A. General measures.

1. Vigorous fluid, electrolyte, and blood replacement must be instituted early in the resuscitative effort, because hemodynamic instability is typical. Intensive-care-unit–level monitoring is recommended.
a. Hypoalbuminemia, persistently elevated acute-phase reactants, small bowel ileus, and deep colonic ulcers are poor prognostic factors for successful medical therapy.
b. Total body potassium depletion is common and needs urgent repletion; phosphate, magnesium, and calcium deficiency also should be corrected parenterally.

2. Oral intake is discontinued, and nasogastric suction is employed for small bowel ileus.
3. Anticholinergic and narcotic agents should be stopped immediately.

4. Serial abdominal exams should be done to assess for signs of deterioration or improvement. Serial abdominal x-rays may also be of value in some cases.
5. Stress ulcer prophylaxis and prophylaxis against deep venous thrombosis should be considered.

B. Treatment of inflammatory bowel disease.

1. When inflammatory bowel disease is diagnosed or suspected, use of parenteral corticosteroids is essential.
   a. Augmented doses (hydrocortisone, 100 mg every 6 hours, or methylprednisolone, 6 to 15 mg every 6 hours) should be administered. A continuous infusion can help maintain steady plasma levels.
   b. Aminosalicylates (e.g., mesalamine, sulfasalazine) have no role in the treatment of fulminant colitis or toxic megacolon and should be withheld until the patient has recovered and has resumed eating.
   c. Adrenocorticotropic hormone may be used in patients who have not had corticosteroid therapy in the last month; however, this is used rarely.
2. Intravenous cyclosporine (2 to 4 mg/kg/24 h in a continuous infusion) can be used when there is no improvement of severe ulcerative colitis after 7 to 10 days of intensive intravenous steroid therapy. The role of cyclosporine in toxic megacolon is controversial.
3. The role of infliximab in severe-to-fulminant ulcerative colitis continues to evolve. Most clinicians would consider infliximab infusion in steroid-refractory severe colitis, but it is important not to delay definitive surgery when toxic megacolon is suspected.

C. Antibiotics.

1. Broad-spectrum antibiotics are administered intravenously once toxic megacolon or transmural inflammation is suspected and are continued until the patient stabilizes over several days to a week. Antibiotics may reduce septic complications and provide coverage in the event of perforation.
2. Broad-spectrum antibiotics should be followed by pathogen-specific therapy in infectious colitis.
3. Intravenous metronidazole (500 mg every 8 hours) or oral/nasogastric vancomycin (500 mg four times daily) should be used if *C. difficile* infection is considered likely from the clinical presentation or proctoscopic findings. This should be accompanied by discontinuing any unnecessary antibiotics.

D. Surgical indications.

1. Surgery is indicated if clinical deterioration or no significant improvement occurs despite 12 to 24 hours of intensive medical management. Delay of operative therapy may promote higher mortality.
2. In ulcerative colitis, failure to respond to parenteral steroids or intravenous cyclosporine after 7 days of therapy is an indication for surgery.
3. Evidence of colonic perforation, uncontrollable bleeding, and progressive dilation are unequivocal indications for emergency surgery.

4. Other indications for emergency surgery include signs of septic shock and imminent transverse colon rupture (the most dilated region in most cases of toxic megacolon), especially if the diameter is >12 cm.
   a. The absence of acute colonic dilatation may permit delay of surgical intervention for 5 to 7 days.
   b. The potential for prolonged intensive medical management and complications must be balanced against early surgical intervention to reduce mortality and morbidity.
5. Surgical options.
   a. The type of surgery performed for the treatment of fulminant colitis or toxic megacolon depends on the clinical status of the patient and the experience of the surgeon.
   b. Most surgeons prefer a limited abdominal colectomy with ileostomy, leaving the rectosigmoid as a mucous fistula, or oversewing the rectum using a Hartmann procedure. This leads to a decreased morbidity and perioperative morality in ill patients, while leaving the option for a subsequent sphincter-saving ileoanal anastomosis.
   c. In less acutely ill patients, a one-stage resection with ileostomy may be appropriate.

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77 Hepatic Dysfunction

Kevin M. Korenblat

I. GENERAL PRINCIPLES

A. Hepatic dysfunction in the intensive care unit (ICU) setting can present as one of the following:

1. Abnormalities of liver chemistries or synthetic function.
2. Signs and symptoms of liver disease (e.g., jaundice, synthetic dysfunction, and complications of portal hypertension).

B. Hepatic metabolic processes are commonly disturbed in the setting of critical illness. These processes and their normal physiology include the following:

1. Bilirubin metabolism.
   - **a.** Bilirubin is the end product of the catabolism of heme, the prosthetic moiety of hemoglobin, myoglobin, and other hemoproteins.
   - **b.** Heme from senescent erythrocytes is the source of 80% of bilirubin.
   - **c.** Unconjugated bilirubin is transported bound to albumin to the liver.
   - **d.** Bilirubin is made soluble by conjugation with glucuronic acid within the hepatocytes.
   - **e.** Conjugated bilirubin is transported into the bile canaliculus and from the bile duct into the intestine.
2. Drug metabolism.
   - **a.** The liver is frequently a site of first-pass metabolism of medications and other xenobiotics.
   - **b.** Metabolic processes can be categorized as phase I or phase II reactions.
     - **i.** Oxioreductases and hydrolases catalyze phase I reactions that increase water solubility of substances and potentially generate toxic metabolites.
     - **ii.** Transferases catalyze phase II reactions that produce biologically less active metabolites.
3. Hemostasis.
   - **a.** The liver is the site of production of many of the vitamin K–dependent coagulation factors and the anticoagulants protein C and protein S.

II. ETIOLOGY

A. Clinical disorders commonly encountered in the critical care setting that result in hepatic dysfunction include the following:

1. Ischemic hepatitis (Table 77-1).

TABLE 77-1 Causes of Ischemic Hepatitis

Hypovolemic shock
Burns
Hemorrhage
Cardiogenic shock
Hypoxemia
Sepsis
Sickle cell crisis
Hepatic artery occlusion; especially post liver transplantation
Heat stroke

a. Develops in the setting of reduced liver blood flow, persistent hypotension, or severe hypoxemia.
b. A clearly defined period of hypotension may not be identifiable.
c. A variable degree of central vein (zone 3) necrosis and collapse are present on liver histology.

2. Congestive hepatopathy.
a. Any process that increases hepatic vein pressures (e.g., right heart failure, pericardial disease, or pulmonary hypertension) can cause hepatic congestion.
b. Mild elevations in serum aminotransferases, alkaline phosphatase, and bilirubin may be present.
c. Long-standing hepatic venous congestion may result in cirrhosis (cardiac cirrhosis).
d. Alternate diagnoses that may resemble the presentation of congestive hepatopathy include the following:
i. Budd-Chiari syndrome (hepatic vein thrombosis).
ii. Sinusoidal obstruction syndrome (venoocclusive disease).
iii. Inferior vena cava thrombosis at its hepatic portion (obliterative hepatocavopathy).

3. Total parenteral nutrition (TPN)–related liver injury.
a. Hepatic steatosis and steatohepatitis are the most common hepatic complications in adults.
b. Asymptomatic elevations in serum chemistries are a common presentation of hepatic steatosis and steatohepatitis.
i. Deficiencies of essential fatty acids (linoleic acid) or choline may contribute to the development of steatosis.
c. Cholestasis is the predominant clinical finding in infants.
i. Conditions associated with the development of cholestasis include large doses of lipid emulsion (>1 g/kg/d), short gut syndrome, and bacterial overgrowth.
ii. Elevations in serum bilirubin may be mild to severe.
iii. Cholestasis, particularly in infants, may result in progression to cirrhosis and liver failure.
d. Biliary sludging.

i. Biliary sludging may develop in up to 50% of patients managed with 6 weeks of TPN.
ii. Clinical manifestations of sludging may vary from asymptomatic to cholecystitis.

4. Sepsis.
   a. Hepatic dysfunction is common in sepsis and is a consequence of alterations in hepatic blood flow, activation of reticuloendothelial cells, and release of inflammatory cytokines.
   b. Elevations in serum aminotransferases two to three times the upper limits of the reference range may occur 2 to 3 days after the onset of bacteremia.
   c. Jaundice with elevations in serum levels of alkaline phosphatase may also occur and is known as sepsis-induced cholestasis. These elevations may become very high, particularly in human immunodeficiency virus (HIV)-1–infected patients.
5. Drug hepatotoxicity.
   a. There are a myriad of patterns associated with drug-induced liver injury. The pattern observed may depend on the dose and duration of drug exposure and host susceptibility factors.
   b. Idiosyncratic reactions (e.g., isoniazid, phenytoin): The damage is dose independent and unpredictable.
   c. Intrinsic hepatotoxicity is dose dependent, as is seen with acetaminophen and methotrexate.

III. DIAGNOSIS

A. History.

1. Pertinent historical features include episodes of symptomatic hypotension, a history of right or biventricular heart failure, and new medications associated with liver injury.
2. Concurrent symptoms of abdominal or right upper quadrant abdominal pain may suggest mechanical biliary obstruction.
3. The history should be scrutinized for the use of nonprescription medications, including complementary and alternative medicines.

B. Physical examination.

1. Physical findings associated with congestive hepatopathy include jaundice, tender hepatomegaly, jugular venous distension, edema, and, in severe cases, ascites.

C. Laboratory studies.

1. In ischemic hepatitis, serum aminotransferases tend to rise rapidly to levels 10 to 40 times the upper limits of the reference range. Increases in alkaline phosphatase and bilirubin may rise as transaminase elevations decrease.

2. Hyperbilirubinemia should be further investigated by measuring both direct-reacting (conjugated) bilirubin and indirect-reacting (unconjugated) bilirubin. The latter is calculated by subtracting the direct fraction from the total bilirubin.
   a. Indirect hyperbilirubinemia may result from hemolysis, decreased hepatic clearance due to impairment of bilirubin conjugation, or circumstances in which both processes occur simultaneously.
      i. Gilbert syndrome and Crigler-Najjar syndrome types I and II are inherited disorders resulting in decreased bilirubin conjugation.
      ii. Gilbert syndrome affects 8% of the general population and is characterized by a mild, unconjugated hyperbilirubinemia to levels that rarely exceed 4 mg/dL and normal liver function.
   b. Mixed direct and indirect hyperbilirubinemia or pure direct hyperbilirubinemia can be the result of heritable disorders of bilirubin canalicular excretion, liver disease, or biliary obstruction.

D. Radiographic studies.

1. Sonography (with Doppler studies) of the right upper quadrant can provide information about liver architecture; diameter of intrahepatic and extrahepatic bile ducts; and flow in hepatic veins, portal vein, and hepatic artery.
2. Combined right heart and transjugular portal pressure measurements can differentiate ascites development from chronic passive congestion from hepatic cirrhosis.

IV. TREATMENT

A. Treatment of ischemic hepatitis and congestive hepatopathy is supportive in nature; emphasis should be placed on maintaining organ perfusion and improving venous return.

B. The cholestasis of sepsis is best managed by treatment of the underlying infectious process, correction of fluid and electrolyte imbalances, and introduction of enteral feeding as soon as the clinical condition permits.

C. TPN steatosis may be amenable to decreasing the carbohydrate load, decreasing total calories (25 to 40 kcal/kg/d), and cycling the infusion schedule.

D. Ursodeoxycholic acid (10 to 45 mg/kg/d) orally has been of variable success in the management of TPN-related cholestasis.

E. Immediate cessation of the medication responsible for liver injury is the treatment of drug-induced liver injury.

1. The development of jaundice in drug-induced liver injury is associated with a 10% to 50% case fatality rate and should prompt consideration for liver transplantation in the appropriate candidate for organ transplantation.

F. Treatment with corticosteroids can be considered in drug hypersensitivity syndromes (drug rash with eosinophilia and systemic symptoms [DRESS]) or drug-induced autoimmune reactions (e.g., minocycline).

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78 Evaluation and Management of Liver Failure

Kevin M. Korenblat

I. GENERAL PRINCIPLES

A. Acute liver failure (ALF), also known as fulminant hepatic failure, is a rare condition defined as the development of coagulation disturbance and encephalopathy in individuals without cirrhosis and with an illness of <26 weeks duration.

1. Wilson disease and autoimmune hepatitis can be included in this diagnosis when the initial presentation is as an acute illness even if cirrhosis is present.

B. Chronic liver failure results from continuous hepatic injury over a prolonged time period and typically is characterized by the following:

1. Cirrhosis of the liver.
2. Portal hypertension.

II. ACUTE LIVER FAILURE

A. Etiology.

1. The causes of ALF are many (Table 78-1). Identification of the cause of ALF is important for several reasons:
   a. Specific treatments are available.
   b. Infectious causes may have implications for public health and be amenable to postexposure prophylaxis.
   c. Prognosis varies with cause.

2. Acetaminophen overdose is the most common cause of ALF in the United States.
   a. Acetaminophen hepatotoxicity can be the consequence of both intentional and unintentional overdosage.
      i. Hepatotoxicity typically occurs when dosages exceed a threshold of 150 mg/kg body weight.
      ii. Individuals at risk for depletion of intracellular glutathione (e.g., chronic alcohol use) or those with increased cytochrome P-450 2E1 activity (e.g., chronic anticonvulsive exposure) can experience severe hepatotoxicity with doses as low as 3 to 4 g/day.
   b. One-third of overdoses may be unintentional; these unintentional overdosages have been associated with greater morbidity and mortality than intentional overdosages.

TABLE 78-1 Causes of Acute Liver Failure

Acute viral hepatitis
Hepatitis A
Hepatitis B
Hepatitis C
Delta agent
Hepatitis E
Cytomegalovirus
Varicella zoster virus
Adenovirus
Paramyxovirus
Ebstein-Barr virus
Herpes virus
Metabolic disorders
Acute fatty liver of pregnancy
HELLP syndrome
Wilson disease
Reye syndrome
Cardiovascular disorders
Budd-Chiari syndrome
Sinusoidal obstruction syndrome
Cardiovascular shock
Hyperthermia
Drug and toxins
Acetaminophen
Sodium valproate
Isoniazid
Halothane
Amanita phalloides

HELLP, hemolytic anemia elevated liver enzymes, and low platelet count.

3. ALF from viral hepatitis can result from infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus (HEV), and herpes simplex virus (HSV); ALF from hepatitis C is extremely rare.
   a. HAV infection is treated with supportive care.
   b. ALF can occur with acute HBV infection or reactivation of inactive infection. The risk of reactivation should be considered in the immunosuppressed subject.
   c. HSV hepatitis can occur in a variety of subjects: healthy individuals, the immunosuppressed and pregnant women in the third trimester.
      i. HSV hepatitis is typically characterized by very high aminotransferases, though jaundice is unusual (anicteric hepatitis). Prompt treatment of known or suspected cases of HSV hepatitis with acyclovir (5 to 10 mg/kg IV every 8 hours) may be lifesaving.

4. Drug-induced liver injury (DILI) accounts for an estimated 13% of ALF in the United States.

B. Complications.

1. Encephalopathy and cerebral edema.
   a. By definition, all patients with ALF have encephalopathy, with symptoms ranging from subclinical confusion (grade 1) to coma (grade 4).
   b. Cerebral edema occurs in up to 80% of patients with ALF and grade 4 encephalopathy and can result in death from brain herniation.
2. Coagulopathy.
   a. Prolongation of the international normalized ratio (INR) and activated partial thromboplastin time occurs as a consequence of reduced hepatic synthesis of vitamin K–dependent coagulation factors.
3. Cardiorespiratory complications.
   a. Typical hemodynamic changes in ALF mimic distributive shock: increased cardiac output, decreased peripheral oxygen extraction, and low systemic vascular resistance.
   b. The development of arterial hypertension may herald the development of cerebral edema.
4. Renal failure.
   a. Renal failure in ALF can result from acute tubular necrosis, prerenal azotemia, or the hepatorenal syndrome (HRS).
   b. In acetaminophen overdosage, acute tubular necrosis from the effect of the toxic metabolite on the kidney can be observed in as many as 75% of cases.
5. Metabolic disorders.
   a. Lactic acidosis develops as the combined consequence of tissue hypoxia with increased lactate production and impaired hepatic metabolism of lactate. Renal dysfunction also may contribute.
   b. Hypoglycemia occurs as a consequence of the loss of hepatic gluconeogenesis and glycogenolysis and signifies severe hepatocellular injury.
6. Infection.
   a. The most common organisms isolated include *Staphylococcus*, *Streptococcus*, gram-negative enteric organisms, and *Candida* spp.
   b. Fungal infections occur late in the course of illness and are associated with high mortality.
   c. Signs of infection can be protean; one-third of septic subjects may be a febrile and lack leukocytosis.

C. Treatment.

1. General measures.
   a. Early identification of the cause of ALF is critical.
   b. Laboratory assessment of hepatic synthetic function, renal function, and acid–base status provides useful prognostic information.
   c. Invasive hemodynamic monitoring is useful in the management of hemodynamic changes associated with ALF.

2. Sepsis.
   a. Surveillance cultures of blood, sputum, and urine should be collected with a low threshold for the use of empiric antibacterial and/or antifungal therapy; the use of prophylactic antibiotics remains controversial.
3. Coagulopathy: The correction of the coagulopathy with fresh frozen plasma (FFP) or platelet transfusion should be reserved for active bleeding or prevention of bleeding during invasive procedures, as excessive blood product transfusion may worsen cerebral and pulmonary edema.
   a. Administration of vitamin K is safe but often ineffective.
   b. Parenteral administration of recombinant factor VIIa may reverse the coagulopathy and is helpful when there is a need to avoid the large volumes associated with FFP.
4. Encephalopathy and cerebral edema.
   a. Frequent neurologic examination, including assessment of level of alertness, pupillary response to light, and motor reflexes, is important in the assessment of encephalopathy and intracranial pressure (ICP).
   b. Avoidance of excessive oral suctioning and visual and auditory stimuli may prevent sudden increases in ICP; nursing with head of bed at >30-degree elevation may improve cerebral venous drainage.
   c. Placement of an ICP monitor is appropriate for the identification and treatment of cerebral edema in subjects who are candidates for liver transplantation (LT) and progress beyond grade 2 encephalopathy.
      i. The cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and ICP; the goal of ICP monitoring is to maintain the CPP > 50 mm Hg and ICP < 15 mm Hg.
      ii. Risks of ICP monitoring include epidural and intracranial bleeding and infection.
   d. Treatment options for increased ICP include the following:
      i. Permissive hypernatremia.
      ii. Hypertonic saline to raise serum sodium to 145 to 155 mmol/L.
      iii. Intravenous (IV) mannitol (0.5 to 1 g/kg).
      iv. Hypothermia to a core body temperature of 32°C.
      v. Hyperventilation to maintain an arterial carbon dioxide partial pressure 25 to 30 mm Hg; the effects are short-lived.
      vi. The use of lactulose in the encephalopathy of ALF is controversial. No clear benefits to severity of encephalopathy or outcome have been shown with its use.
5. Metabolic disorders.
   a. Hemodialysis may be required. Continuous modes of hemodialysis are preferable to prevent hemodynamic instability.
   b. Prevention of hypoglycemia is essential for preservation of neurologic function; frequent glucose monitoring and infusions of 10% to 50% dextrose solutions may be required.
6. Acetaminophen toxicity. The administration of *N*-acetylcysteine (NAC) is an effective, lifesaving antidote to acetaminophen toxicity.
   a. The decision to use NAC is based on reference to a standardized treatment nomogram and requires knowledge of serum acetaminophen level and time of ingestion.

b. NAC is most effective when given within the first 24 hours after ingestion; NAC may still be useful even when treatment is delayed >24 hours or when signs and symptoms of ALF have developed.

c. The oral dose of NAC is 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 hours.

d. NAC can be given as a continuous IV infusion, and various dosing regiments are available. One dosing schedule is 150 mg/kg IV given over 15 minutes, followed by 50 mg/kg IV given over 4 hours, and then 100 mg/kg IV given over 20 hours.

e. Electrolyte imbalances, particularly hypophosphatemia, are common with acetaminophen-induced liver failure and correction of electrolyte disorders is essential.

7. Role of NAC in nonacetaminophen ALF.

a. In a randomized, controlled trial, administration of NAC to subjects with nonacetaminophen ALF appeared to improve spontaneous survival when given during the early stages of encephalopathy.

8. LT: Patients with ALF without contraindications to LT should be managed at LT center.

a. The King's College criteria (Table 78-2) can be useful to identify poor prognostic factors that identify individuals who require LT for survival. These criteria are subdivided into acetaminophen and nonacetaminophen causes of ALF.

i. Currently available scoring systems do not adequately predict outcome and should not be exclusively relied upon to determine need for LT.

TABLE 78-2 King's College Criteria for Liver Transplantation for Acute Liver Failure (ALF)

Nonacetaminophen causes of ALF
INR > 7.7 (irrespective of grade of encephalopathy) or any three of the following:
- Age <10 or >40
- Unfavorable cause
  - Non-A, non-B hepatitis
  - Drug reaction
  - Wilson disease
- Period of jaundice to encephalopathy >7 days
- INR > 3.85
- Serum bilirubin > 17 mg/dL

Acetaminophen-related ALF
pH < 7.3 (irrespective of grade of encephalopathy) or all three of the following
- Grade III–IV encephalopathy
- INR > 7.7
- Serum creatinine > 3.4 mg/dL

INR, international normalized ratio.

TABLE 78-3 Causes of Chronic Liver Failure

Hepatitis B
Hepatitis C
Autoimmune hepatitis
Hereditary hemochromatosis
α_1-Antitrypsin deficiency
Wilson disease
Nonalcoholic fatty liver disease
Primary biliary cirrhosis
Primary sclerosing cholangitis
Alcohol-related liver disease

III. CHRONIC LIVER FAILURE

A. Etiology.

1. Chronic liver failure is the consequence of long-standing hepatic injury from multiple different causes (Table 78-3).

B. Pathophysiology.

1. Cirrhosis also results in endothelial dysfunction and increased resistance to flow within the hepatic sinusoids. Sinusoidal hypertension and endothelial dysfunction produce portal hypertension and its cardinal features.
   a. Increased resistance to mesenteric vascular flow.
   b. Activation of the compensatory systems to maintain effective arterial volume resulting in sodium and water retention and increased intravascular volume.
2. Portal hypertension is responsible for many complications of chronic liver disease:
   a. Gastrointestinal bleeding.
   b. Ascites.
   c. Portosystemic encephalopathy.
   d. HRS.
   e. Pulmonary disease.
      i. Hepatopulmonary syndrome.
      ii. Portopulmonary hypertension.

C. Diagnosis.

1. History.
   a. Common symptoms include fatigue, increased abdominal girth, emotional lability, day–night sleep reversal, and poor mental concentration.
2. Physical examination.
   a. Common physical findings include jaundice, temporal wasting, abdominal ascites, splenomegaly, asterixis, spider angiomata, and male gynecomastia.

3. Blood tests.
   a. Varying degrees of thrombocytopenia and leucopenia may be present as a consequence of hypersplenism.
   b. Anemia associated with liver disease is typically macrocytic. In advanced liver disease, a spur cell (acanthocytes) hemolytic anemia may develop.
   c. Elevations in serum transaminases and alkaline phosphatase are variable; hypoalbuminemia and prolongation of INR are common with cirrhosis and indicate synthetic dysfunction.
   d. A mixed direct- and indirect-reacting hyperbilirubinemia is common, particularly in cholestatic liver diseases.
   e. Elevations in serum ammonia are commonly seen with encephalopathy; however, there is modest correlation with the magnitude of the elevation and the severity of the encephalopathy.
4. Ascites studies.
   a. Ascites from portal hypertension is characterized by a difference >1.1 g/dL between serum albumin and ascites albumin; this difference is known as the serum–ascites albumin gradient (SAAG).
   b. Spontaneous bacterial peritonitis (SBP) is diagnosed when the neutrophil count in ascites fluid is >250/mL or when bacteria can be cultured from ascites.
   c. The ascites fluid should be inoculated directly into blood culture bottles to increase the potential for identification of bacteria.
   d. Peritonitis from either abdominal perforation or nonperforation abdominal abscess should be considered when multiple organisms are cultured from the ascites or the neutrophil count is high.
      i. The ascites in these conditions should fulfill two of the following criteria:
         (a) Total protein > 1g/dL.
         (b) Glucose < 50 mg/dL.
         (c) LDH greater than upper limit of the reference range.
5. Urine studies.
   a. A random urine sodium <20 mmol/L is typical but not required for the diagnosis of HRS.

D. Treatments.

1. Ascites.
   a. Dietary sodium restriction to <2 g daily is the first-line treatment of ascites.
   b. The combination of furosemide (20 to 160 mg daily) and spironolactone (50 to 400 mg daily) is effective in the control of ascites in most cases; IV diuretics should be avoided and may precipitate renal failure.
   c. Intermittent large-volume paracentesis or transjugular intrahepatic portosystemic shunt (TIPS) is an alternative measure for the control of ascites refractory to diuretics or in those intolerant of diuretics (e.g., hyponatremia, renal insufficiency).
2. Spontaneous bacterial peritonitis.

   a. The antibiotics of choice in the absence of bacteriologic identification are the IV third-generation cephalosporins effective against gram-negative enteric organisms.
   b. IV albumin (1.5 g/kg on day 1 and 1 g/kg on day 3) can reduce rates of infection-related renal dysfunction from 30% to 10%.

3. Encephalopathy.
   a. Patients should be investigated for precipitants of encephalopathy, including gastrointestinal hemorrhage, infection, and renal failure.
   b. Lactulose orally (15 to 60 mL every 4 to 12 hours) titrated to three to four soft bowel movements per day is effective in most cases of encephalopathy.
   c. The addition of rifaximin (550 mg every 12 hours) to lactulose reduces the frequency of episodes of encephalopathy.
4. Variceal hemorrhage (see Chapter 74).
5. Hepatorenal syndrome.
   a. Diuretics should be discontinued.
   b. Volume replacement with IV saline 1.5 L should be given.
   c. IV albumin 25 to 75 g daily may be more effective in expanding intravascular volume.
   d. A small series suggests a role for octreotide subcutaneously (100 μg) every 8 hours, midodrine (7.5 to 12 mg) every 8 hours, and IV albumin for treatment of HRS.
   e. The development of HRS should prompt consideration for LT in appropriate subjects.
6. Pulmonary disease.
   a. Hepatopulmonary syndrome.
      i. A disorder characterized by portal hypertension (with or without cirrhosis), arterial hypoxemia (A-a gradient >15 mm Hg on room air), and evidence of pulmonary vascular dilation.
      ii. Contrast-enhanced echocardiography typically demonstrates the delayed (>3 cardiac cycles) passage into the left heart of injected agitated saline bubbles.
      iii. Supplemental oxygen administration, exclusion of other causes of shunt, and LT are treatments.
   b. Portopulmonary hypertension.
      i. A disorder characterized by liver disease causing portal hypertension, mean pulmonary arterial pressure (PAP) > 25 mm Hg (at rest), mean pulmonary capillary wedge pressure < 15 mm Hg, and pulmonary vascular resistance >3 Woods units.
      ii. Right heart catheterization with measurement of pulmonary artery pressure is the "gold standard" for diagnosis.
      iii. LT is contraindicated in subjects with severe pulmonary hypertension (mean PAP > 50 mm Hg) but can be considered in those who respond to treatment with oral or IV vasodilator therapy.
7. Liver transplantation.
   a. LT in appropriately selected subjects can effectively treat all the complications of end-stage liver disease.

b. In the United States, prioritization for LT is determined by calculation of the model for end-stage liver disease (MELD) score. A MELD calculator is available at URL: http://www.unos.org/resources/ meld-PeldCalculator.asp.

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79 Diarrhea

Kara A. Regan and C. Prakash Gyawali

I. GENERAL PRINCIPLES

A. Definition.

1. Diarrhea is traditionally defined as increase in frequency of stool or decrease in consistency, based upon the individual's baseline.
2. Other definitions include three or more loose or watery stools per day and stool weight > 200 g/day.

B. Classification.

1. Acute diarrhea consists of diarrhea lasting ≤14 days.
2. Chronic diarrhea is defined as diarrhea continuing for >30 days. Diarrhea lasting >14 days but <30 days is sometimes termed persistent diarrhea.

C. Epidemiology.

1. Food- and water-borne gastroenteritis accounts for most cases of acute diarrhea, approximately 89 million cases per year. Risk factors include sick contacts, pregnancy, travel, well water, pets, immunosuppression, HIV, homosexual males, and day care exposure. Non–food- or water-borne illness accounts for 122 million cases per year.
2. The prevalence of chronic diarrhea in the United States is estimated to be 5%.
3. Diarrhea is a frequent complication in critically ill patients occurring in 40% to 50% of patients in the intensive care unit (ICU). If untreated, it can produce serious fluid and electrolyte imbalance, skin breakdown, local infection, and difficulty with nutritional management.
4. Diarrhea is listed as a cause of death in over 3,000 people per year in the United States. The mortality in the elderly (>60 years) can be as high as 85%.

II. ETIOLOGY

A. Infectious causes.

1. Typical etiologies in the community may also apply to the patient in intensive care. The most commonly reported cause of acute gastroenteritis in the community is norovirus (Norwalk); other viral etiologies include rotavirus, enteric adenovirus types 40 and 41, and astrovirus. *Salmonella* and *Campylobacter* are common bacterial causes. Bloody diarrhea can typically result from *Shigella* and *Escherichia coli* O157:H7 infections. Amebiasis can also cause bloody diarrhea and dysentery.

Fungal and mycobacterial diarrhea are rare. Brainerd diarrhea is a chronic or persistent cause of diarrhea of rather acute onset but unclear etiology, first reported in Brainerd, Minnesota.

2. *Clostridium difficile* toxin–induced colitis is implicated in 15% to 20% of cases. Clindamycin, penicillin, and broad-spectrum cephalosporins are commonly associated with the diagnosis.
3. In the immunosuppressed and the elderly, cytomegalovirus (CMV) or herpes simplex virus (HSV) may be implicated.

B. Iatrogenic causes.

1. Medications.
   a. Antibiotics, especially erythromycin, ampicillin, clindamycin, cephalosporins, and azithromycin, cause iatrogenic diarrhea in 3% to 29% of patients. Alterations in intestinal flora, breakdown of dietary carbohydrate products, and prokinetic effects (e.g., from erythromycin) are all postulated mechanisms for antibiotic-related diarrhea.
   b. Other medications implicated in the development of diarrhea include antacids (magnesium containing), magnesium and phosphorus supplements, lactulose, colchicine, digitalis, quinidine, theophylline, levothyroxine, aspirin, nonsteroidal anti-inflammatory agents, cimetidine, misoprostol, diuretics, β-blocking agents, chemotherapeutic agents, proton-pump inhibitors, and antiretroviral medications such as nelfinavir. These medications rarely cause severe diarrhea.
2. Enteral feeding.
   a. Diarrhea frequently occurs in enterally fed patients and is usually associated with concurrent antibiotic use.
   b. Osmolarity of the enteral solution can play a role in some instances, as can bolus feeding distal to the pylorus.
   c. Enteral formulas high in lactose or fat content may precipitate diarrhea in susceptible patients.

C. Diarrhea as a primary manifestation of disease.

1. **Inflammatory bowel disease (IBD):** The two named IBDs are Crohn's disease, which can affect any part of the luminal gut; and ulcerative colitis, which only affects the colon within the luminal gut. Less common patterns of inflammatory mucosal disease include lymphocytic colitis, collagenous colitis, autoimmune enteritis, celiac disease, sarcoid, graft-versus-host disease (GVHD), and other idiopathic processes. Fulminant colitis is addressed elsewhere (see Chapter 76).
2. **Malignancy:** Certain types of adenocarcinoma can cause diarrhea, especially those with villous patterns. Lymphoma, carcinoid, gastrinoma, VIPoma, and somatostatinoma can also present as diarrhea.
3. **Anatomical causes:** Short gut syndrome, where <200 cm of functional small intestine remains, can manifest with prominent diarrhea that can be particularly worsened by severe intercurrent illness. Subtotal gastrectomy, roux-en-Y gastric bypass, ileocolonic resection, and subtotal colectomy may also be associated with diarrhea.
4. **Other causes:** This includes sepsis, vasculitis, diabetic diarrhea, renal failure, pancreatic exocrine insufficiency, and adrenal insufficiency.

D. Diarrhea secondary to underlying diseases.

1. Infections, neoplastic disease in immunosuppressed patients, and neutropenic enteropathy.
2. Gastrointestinal (GI) bleeding and ischemic bowel can be associated with diarrhea. Chronic mesenteric ischemia can also manifest as diarrhea.
3. Other causes include fecal impaction and opiate withdrawal.

III. DIAGNOSIS

A. Clinical presentation.

1. History.
   a. Attention to historical data (e.g., onset, duration, character, relation to antibiotic usage, or enteral feeding) may lead to prompt diagnosis and management.
   b. *Clostridium difficile*–related diarrhea may occur up to 8 weeks after the offending antibiotic is discontinued.
   c. Abdominal pain suggests ischemia, infection, or inflammatory conditions, such as vasculitis or GVHD, depending on the clinical setting.
   d. Bloody diarrhea may indicate overt GI bleeding, ischemic colitis, or occasionally pseudomembranous colitis.
   e. Passage of frequent small-volume stools with urgency or tenesmus suggests distal colonic involvement, whereas passage of less-frequent, large-volume stools suggests a more proximal process.
   f. Medication lists and tube feeding formulae should be scrutinized.
2. Physical examination usually is nonspecific and is most helpful in assessing severity of volume loss. Indicators of severe illness may include profuse diarrhea (especially bloody diarrhea), hypovolemia and hypotension, temperature > 38.5°C (101.3°F), severe abdominal pain, older age, immunocompromised state, or pregnancy.
   a. Skin rashes or mucosal ulcerations may suggest GVHD, IBD, or vasculitis; other extraintestinal manifestations of diseases associated with diarrhea should be noted.
   b. Postural hypotension suggests severe volume loss, adrenal insufficiency, or autonomic neuropathy.
   c. Fever suggests possible infection, vasculitis, adrenal insufficiency, or hyperthyroidism.
   d. Abdominal tenderness may suggest infection, ischemia, or vasculitis.
   e. An abnormal rectal examination may be the only sign of a partially obstructing fecal impaction.

B. Laboratory studies.

1. Hyperchloremic metabolic acidosis, hypokalemia, prerenal azotemia, and other serious electrolyte imbalances may occur with severe diarrhea. Hyperkalemia may be present with adrenal insufficiency or uremia.
2. Leukocytosis may suggest infection or ischemia, neutropenia, an immunosuppressed state, or sepsis. A falling hematocrit may suggest GI bleeding.

3. Additional tests can include TSH, celiac serology, urine 5-HIAA and serum chromogranin (carcinoid), serum vasoactive intestinal peptide (VIPoma), serum gastrin (gastrinoma), somatostatin (somatostatinoma), serum calcitonin, stool magnesium and laxative screen (laxative abuse), and antienterocyte antibody (autoimmune enteropathy).

C. Stool studies.

1. Fresh stool specimens should be sent for *C. difficile* toxin assay and culture for enteric pathogens. Stool PCR for *C. difficile* is rapidly replacing the toxin assay because of its superior sensitivity, specificity, and rapid turnover. Repeat tests are unnecessary; however, the test may remain positive for an indeterminate amount of time.
2. Immunosuppressed patients may need more extensive stool tests, including ova and parasite evaluation and concentration for isolation of *Cryptosporidium*, *Microsporidium*, or *Isospora belli.*
3. The stool osmolar gap, that is, the difference between the expected stool osmolarity (290 mOsm/kg) and the calculated stool osmolarity {([stool Na^+] + [stool K^+]) × 2}, may help distinguish between osmotic and secretory causes when diarrhea is severe or protracted and no diagnosis is apparent; an elevated stool osmolar gap (>70 mOsm/L) suggests osmotic causes.
4. High-volume stool output that persists with fasting supports a secretory origin.
5. A Sudan stain for fecal fat or stool pH occasionally is helpful (pH <5.6 may indicate carbohydrate malabsorption).

D. Imaging studies.

1. Plain abdominal radiographs can detect partial obstruction, perforation, or changes associated with enteritis or colitis and are recommended in the presence of pain or an abnormal abdominal examination.
2. Contrast studies, including computed tomography (CT) and intestinal radiographs, may be required in difficult or protracted cases, when possible. CT imaging can help identify bowel wall thickening, tumors, and obstruction. MREnterography/CTEnterography can assist with better examination of the small bowel for abnormality and IBD. Small bowel follow-through can help better define the anatomy of the small bowel, and examine for evidence of small bowel abnormality or fistula.

E. Endoscopy.

1. Flexible sigmoidoscopy is useful in diagnosing pseudomembranous colitis, ischemic colitis, CMV colitis, herpetic proctocolitis, or GVHD and is usually considered in the presence of bright red rectal bleeding or other indicators of distal colitis.
2. Mucosal biopsies are helpful on occasion when endoscopic findings are nonspecific or absent. Colonoscopy is most useful in chronic diarrhea for the identification of IBD, microscopic inflammatory disorders, and neoplasia. Upper endoscopy with small bowel biopsies may be of value to evaluate in diagnosing celiac disease, giardiasis, Crohn disease, Whipple disease, amyloid, and eosinophilic gastroenteritis. Duodenal aspirate could have value in diagnosing *Giardia* or small intestinal bacterial overgrowth.

IV. TREATMENT

A. General measures.

1. Correction of fluid and electrolyte imbalance needs immediate attention.
2. Central venous access and monitoring may be necessary in patients with severe fluid loss.
3. Proper patient hygiene and skin care should be maintained, and patient isolation with enteric precautions should be instituted when indicated.
4. Iatrogenic causes of diarrhea are corrected by withdrawal of the offending medications.
5. Enteral feedings suspected of causing diarrhea should be reduced in volume or temporarily discontinued. Some suggest an advantage of continuous infusion over bolus infusions. There is also evidence to suggest that the addition of fiber to continuous infusions decreases the incidence of diarrhea in tube-fed patients.
6. A change in formula to an elemental diet may be indicated in patients with short bowel syndrome, pancreatic insufficiency, radiation enteritis, fistula, or IBD.
7. In severe cases, total parenteral nutrition may be necessary as a temporary measure.

B. Specific treatment.

1. Specific or pathogen-related treatment should be administered whenever possible in both immunocompromised and immunocompetent hosts.
2. *Clostridium difficile* colitis.
   a. If *C. difficile*–related diarrhea is suspected, the offending antibiotic should be discontinued when possible; spontaneous improvement often results from this measure alone; 15% to 23% of patients have symptom resolution within 48 to 72 hours of stopping the offending agent. Unfortunately, this option is often not possible in the intensive care setting, as it is not possible to predict which patients will respond with spontaneous resolution with simple cessation of the antibiotic, and delaying therapy increases the period of contagion.
   b. Earlier studies indicated that oral metronidazole (250 to 500 mg three times daily) was as effective as oral vancomycin (125 to 500 mg four times daily), yet was less expensive and did not contribute to selection for vancomycin-resistant bacteria. In moderate to severe cases of *C. difficile* colitis, however, more recent studies have suggested that oral metronidazole may be inferior to vancomycin.
   c. Vancomycin is typically reserved for treatment failures and severe cases. However, in toxic megacolon, intravenous metronidazole should be administered.
   d. Response is expected within 24 to 48 hours with improvement in diarrhea, pain, fever, and leukocytosis. Treatment should be continued for 7 to 14 days.
   e. As many as 24% patients have a relapse and, in these situations, longer and multiple courses of treatment are often required.

f. Anion-exchange resins such as cholestyramine or colestipol are reportedly useful as adjunctive measures in mild cases or in relapses. These agents can bind vancomycin, making their use less desirable.

g. Antimotility agents should not be used, because they may lengthen the course of the illness.

C. Symptomatic measures.

1. When a cause of diarrhea is not found, palliative treatment lessens fluid losses, patient discomfort, and morbidity.

2. Antimotility agents may decrease the frequency and severity of diarrhea, but monitoring for complications is required (e.g., central nervous system side effects, gut hypomotility).

a. These drugs include loperamide (4 mg initially, and up to 16 mg/day), diphenoxylate with atropine (20 mg of diphenoxylate four times daily initially, then decrease and titrate to symptoms), and deodorized tincture of opium (6 to 12 gtt two to four times daily).

b. Octreotide can be used for palliation of diarrhea in patients with acquired immunodeficiency syndrome, GVHD, hormone-producing tumors, and other causes of secretory diarrhea.

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80 Severe and Complicated Biliary Tract Disease

Tarek Abou Hamdan and Riad Azar

I. GENERAL PRINCIPLES

A. Timely diagnosis and therapy of the different biliary disorders commonly encountered in the intensive care unit (ICU) reduce the significant mortality and morbidity from unrecognized disease.

B. A practical approach to evaluate and treat biliary disorders using a wide array of noninvasive and invasive diagnostic and therapeutic aids is of paramount importance.

II. ETIOLOGY

A. Cholangitis.

1. Cholangitis occurs in patients with bile duct obstruction from stones, strictures, or recent manipulation of the biliary tree promoting bacterial translocation.
2. The clinical manifestations include fever, right upper quadrant (RUQ) abdominal pain, and jaundice (Charcot triad). In severe cases, mental status changes and hypotension can be present (Reynold pentad).
3. Laboratory abnormalities include elevated bilirubin, alkaline phosphatase, and white cell count.
4. Blood cultures are often positive for gram-negative bacteria and anaerobes.

B. Biliary obstruction without cholangitis.

1. Common causes include stone disease, benign strictures, and tumors; other causes are listed in Table 80-1.
2. When the obstruction is painless, the most likely diagnosis is a neoplasm.

C. Bile leak.

1. Bile leak can result from cholecystectomy, hepatic resection, liver transplantation, trauma, or percutaneous biliary manipulations.
2. The resultant bile peritonitis produces abdominal pain, ascites, leukocytosis, and fever.

D. Acalculous cholecystitis.

1. Acalculous cholecystitis is typically seen in critically ill patients and can result in significant morbidity and mortality.
2. High degree of suspicion is needed because symptoms may be masked by the underlying clinical situation.

TABLE 80-1 Causes of Biliary Obstruction

Intrinsic lesions
Gallstones
Cholangiocarcinoma
Benign stricture
Sclerosing cholangitis
Periarteritis nodosa
Ampullary stenosis
Parasites
Extrinsic lesions
Pancreatic carcinoma
Metastatic carcinoma
Pancreatitis
Pancreatic pseudocyst
Visceral artery aneurysm
Lymphadenopathy
Choledochal cyst
Hepatic cyst or cysts
Duodenal diverticulum
Iatrogenic lesions
Postoperative stricture

E. Gallstone pancreatitis.

1. Evidence suggests that stone passage or impaction in the ampulla leads to pancreatitis.
2. The severity of pancreatitis can be graded based on prognostic scales that include the Ranson criteria, the Glasgow criteria, and computed tomography (CT) identifying those at risk for a complicated hospital course.

III. DIAGNOSIS

A. Physical examination.

1. Physical examination may reveal icterus, ascites, or focal RUQ tenderness.
2. Findings range from acute abdomen to fever.

B. Laboratory evaluation.

1. Bilirubin elevation may indicate an obstructive process, but can result from sepsis, drugs, or hemolysis in acutely ill patients.
2. Alkaline phosphatase elevation is not specific for biliary disease; concomitant elevation of γ-glutamyl transferase helps confirm hepatobiliary origin.
3. Elevation of transaminases can be seen with bile duct obstruction and may precede bilirubin and alkaline phosphatase elevation in the acute setting.
4. Occasionally, lab values can be normal as in cholecystitis.

C. Plain abdominal radiograph.

1. Usually shows nonspecific findings.
2. Air in the biliary tree can result from a prior sphincterotomy, biliary–enteric fistula or surgical anastomosis, or infection with gas-producing organisms.

D. Ultrasonography.

1. The initial procedure of choice and can be performed at the bedside.
2. Sensitive for determining biliary ductal dilatation, acute cholecystitis, and >95% accuracy in detecting cholelithiasis.
3. Limited accuracy in detecting choledocholithiasis, as gas in the duodenum can obscure visualization of the distal bile duct.

E. Radionuclide scanning.

1. ^{99m}Technetium (^{99m}Tc) hepatic iminodiacetic acid (HIDA) scans yield physiologic and structural information regarding the biliary tract.
2. Filling of the gallbladder confirms patency of the cystic duct virtually excluding acute cholecystitis.
3. Can be false positive in patients on long-term total parenteral nutrition (TPN) or after prolonged fasting.
4. Limited role in patients with poor hepatocellular function, complete biliary obstruction, and cholangitis, each of which prevents adequate uptake or excretion of the radiopharmaceutical into the biliary tree.
5. Evidence of radiotracer in the abdominal cavity is diagnostic of bile leaks.

F. CT and magnetic resonance imaging (MRI).

1. Highly accurate for the detection of level and cause of biliary obstruction.
2. CT allows detailed visualization of the pancreas for grading the severity of pancreatitis and assessing its complications.
3. CT may reveal a biloma or free fluid in the abdominal cavity.
4. MRI that incorporates cholangiopancreatography (MRCP) provides high-resolution images of the pancreatobiliary system with very high sensitivity and specificity for diagnosis of choledocholithiasis, strictures, and tumors.
5. These studies are impractical in many ICU patients who are too sick for transport.

G. Endoscopic ultrasound (EUS).

1. The entire biliary tree and pancreas can be imaged without intestinal gas interference.
2. More sensitive than transabdominal ultrasonography in detecting choledocholithiasis.
3. EUS is an elective procedure and uncommonly used in the ICU.
4. Useful to identify patients who would benefit from endoscopic stone extraction by endoscopic retrograde cholangiopancreatography (ERCP).

IV. TREATMENT

A. Cholangitis and biliary obstruction.

1. If cholangitis is suspected, extended-spectrum antibiotics should be started promptly along with aggressive supportive measures.

2. Emergent ERCP with sphincterotomy and biliary stenting to achieve biliary decompression.

B. Bile leaks.

1. ERCP for biliary decompression and stent placement should be performed immediately to allow the leak site to heal.
2. Broad-spectrum antibiotics protect against sepsis.

C. Acute cholecystitis.

1. IV fluids, antibiotics, and nasogastric suction are the initial therapies.
2. Percutaneous cholecystostomy is an alternative in patients who are too unstable for operative cholecystectomy.

D. Acute gallstone pancreatitis.

1. Majority will improve with conservative therapy.
2. Early ERCP indicated for severe pancreatitis, persistant jaundice, or cholangitis to remove retained common bile duct stones.
3. Definitive therapy with elective cholecystectomy or endoscopic sphincterotomy with stone extraction in nonoperative candidates during initial hospital admission after pancreatitis has subsided to prevent recurrences.

V. COMPLICATIONS

A. Cholangitis and biliary obstruction.

1. If ERCP is unsuccessful, percutaneous transhepatic cholangiography (PTC) should be performed.

B. Bile leaks.

1. Bilomas usually require percutaneous drainage in addition to an ERCP.

C. Cholecystitis.

1. Complications of acute cholecystitis include gall bladder perforation and emphysematous cholecystitis.
2. The cholecystostomy drainage catheter is left in place until acute symptoms resolve.
3. In patients with severe comorbid illnesses, the tube may simply be removed with or without percutaneous stone extraction.

D. Acute gallstone pancreatitis.

1. Tube feedings or TPN is required if symptoms do not resolve within 7 days.
2. Pseudocysts develop in 15% of patients, and bacterial colonization can lead to abscess formation mandating endoscopic, surgical, or percutaneous drainage.

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81 The Basic Principles of Nutritional Support in the Intensive Care Unit

Dominic J. Nompleggi

I. GENERAL PRINCIPLES

A. Severe protein-calorie malnutrition, unfortunately, is common in critically ill patients.

B. In all patients with serious illness, appropriate measures to avoid substrate deficiency and to replete nutrient deficiency are best recognized promptly, and appropriate therapy is instituted without delay.

II. PATHOGENESIS

A. Malnutrition can be present on admission or develop as a result of the metabolic response to injury.

B. Changes in metabolic response are difficult to assess.

C. Assessment includes evaluation of clinical, anthropometric, chemical, and immunologic parameters reflecting altered body composition.

III. DIAGNOSIS

A. General assessment.

1. The purpose of nutritional assessment is to identify the type and degree of malnutrition in order to devise a rational approach to treatment.
2. Percentage weight loss in the last 6 months, serum albumin level, and total lymphocyte count are the commonly used measures to assess nutritional status.
3. Weight loss of 20% to 30% suggests moderate caloric malnutrition, while 30% or greater indicates severe protein-calorie malnutrition; loss of 10% or more over a short period of time is also considered clinically important.
4. The general appearance of the patient, with emphasis on evidence of temporal, upper body, and upper extremity wasting of skeletal muscle mass, provides a quick, inexpensive, and clinically useful measure of nutritional status.

B. Laboratory assessment.

1. Serum albumin measures visceral protein stores; it is a useful and readily available indicator of kwashiorkor (protein malnutrition).
2. Serum albumin is not a sensitive indicator of malnutrition in ICU patients because its synthesis is influenced by numerous factors other

than nutritional status (e.g., protein-losing states, hepatic function, and acute infection or inflammation).

3. Malnutrition is closely correlated with alterations in immune response as measured by skin test reactivity and total lymphocyte count.
4. A total lymphocyte count <1,000/mm^3 is indicative of altered immune function and is associated with decreased skin test reactivity.
5. Loss of skin test reactivity is a measure of impaired cellular immunity, which consistently has been found to be associated with malnutrition.

C. Subjective global assessment.

1. Subjective global assessment (SGA) evaluates nutritional status using clinical parameters such as history, physical findings, and symptoms.
2. The SGA determines whether
   a. nutritional assimilation has been restricted because of decreased food intake, maldigestion, or malabsorption;
   b. any effects of malnutrition on organ function and body composition have occurred; and
   c. the patient's disease process influences nutrient requirements.
3. In hospitalized patients, SGA has been shown to provide reliable and reproducible results with more than 80% agreement when blinded observers assessed the same patient.

IV. TREATMENT

A. Critical depletion of lean tissue can occur after 14 days of starvation in severely catabolic patients.

B. Nutrition support should be instituted in patients who are not expected to resume oral feeding for 7 to 10 days.

C. Enteral feeding.

1. Enteral feeding reduces infection and preserves gut integrity, barrier, and immune function.
2. It is the preferred route of nutrient administration.
3. Current recommendations support initiation of enteral nutrition as soon as possible after resuscitation.
4. The only contraindication is a nonfunctioning gut.
5. Enteral feeding technique.
   a. Initiation of enteral feeding distal to the pylorus does not require active bowel sounds or the passage of flatus or stool.
   b. Small bowel feedings can be given in the presence of mild or resolving pancreatitis and low-output enterocutaneous fistulas (<500 mL/day).
   c. Worsening abdominal distention or diarrhea in excess of 1,000 mL/day requires a medical evaluation; if distention is present, enteral feedings should be discontinued.
   d. If no infectious cause is found for the diarrhea, antidiarrheals can be administered and feedings continued.
   e. Standard isotonic polymeric formulations can meet most patients' nutritional needs.

f. Elemental formulas should be reserved for patients with severe small bowel absorptive dysfunction; specialty formulations have a limited clinical role.

g. Macronutrient goals resemble those for parenteral nutrition (see section IV.D.3 below): protein requirements should be provided first and dictate the total daily volume needed; remaining macronutrients are in fixed proportions, depending on the formulation selected.

D. Parenteral feeding.

1. Parenteral nutrient administration is recommended when the gastrointestinal tract is nonfunctional or inaccessible or enteral feeding is insufficient.

2. Parenteral nutrient admixtures are not as nutritionally complete as enteral formulations, but nutritional goals are achieved more often with the former than the latter.

3. Macronutrients.

a. Energy adequate to promote anabolic functions is essential.

b. Caloric requirements should be based on the usual body weight; a requirement of 25 kcal/kg is adequate for most patients.

c. The protein requirement (1.2–1.5 g/kg/d) should be calculated first to assure protein sparing and maintain lean tissue mass.

d. Next, approximately 15% to 30% of total calories should be given as fat.

e. The remaining calories should be given as a carbohydrate.

4. Micronutrients (vitamins, trace minerals) and fluid.

a. Potassium, magnesium, phosphate, and zinc should be provided in amounts necessary to maintain normal serum levels.

b. Absolute requirements for vitamins, minerals, and trace elements have not yet been determined.

c. Normal serum and blood levels of vitamins have been established but can vary with the laboratory in which the measurement is obtained.

d. In general, patients should receive fluid at 25 mL/kg body weight to avoid dehydration.

e. Glycemic control may reduce mortality.

V. SUMMARY

A. Need for nutritional support is determined by the balance between endogenous energy reserves of the body and the severity of stress.

B. Best clinical markers of stress are fever, leukocytosis, hypoalbuminemia, and a negative nitrogen balance.

C. Enteral route should be used to provide nutrients if the gut is functioning.

D. Provision of energy and protein should be tailored to the individual patient.

E. During illness, hypoalbuminemia should be viewed as a marker of injury and not as an indicator of impaired nutrition; normal concentrations are unattainable in many critically ill patients because of large fluid shifts and acute-phase protein synthesis.

F. Goal of short-term nutritional support is to optimize the body's metabolic response to injury by improving immune function, reducing inflammation, maintaining gut barrier function, and minimizing nitrogen deficit.

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SECTION 8

Endocrine Problems in the Intensive Care Unit

Samir Malkani

82 Management of Hyperglycemia in the Critically Ill Patients

Leslie J. Domalik and David M. Harlan

I. GENERAL PRINCIPLES

A. Hyperglycemia in intensive care unit (ICU) patients is common due to the following:

1. Preexisting diabetes.
2. Undiagnosed diabetes.
3. Stress hyperglycemia.
4. Medications—for example, glucocorticoids, catecholamines.
5. Nutritional support—for example, TPN, continuous enteral tube feeding.

B. Associated problems.

1. Electrolyte disturbances.
2. Impaired immunity.
3. Endothelial dysfunction.
4. Poor wound healing.
5. Increased in-hospital mortality.
6. Congestive heart failure following acute myocardial infarction.
7. Ketoacidosis and hyperosmolar coma in patients with preexisting or undiagnosed diabetes.

II. PATHOPHYSIOLOGY

A. Normal glycemia.

1. Tightly regulated between 70 and 120 mg/dL, depending mostly on appropriate circulating insulin concentrations to regulate glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis.
2. ICU hyperglycemia management achieved by consistent and appropriate "insulinization" *at all times.*

B. Diabetes classification system.

1. **Type 1 diabetes (T1D)**—Formerly designated insulin-dependent, ketosis-prone, or juvenile diabetes.
   a. Caused by autoimmune destruction of insulin-producing pancreatic β-cells producing near-absolute insulin deficiency.
   b. Patients *require* exogenous insulin for survival. Discontinuing insulin therapy, even for brief intervals, leads to serious metabolic complications.
2. **Type 2 diabetes (T2D)**—Formerly designated non–insulin-dependent or adult-onset diabetes.
   a. Caused by relative (not absolute) insulin deficiency due to defects in both insulin action and insulin secretion.
   b. While T2D can typically be treated with diet, oral agents, non–insulin-injectable agents, or insulin, insulin is the most appropriate treatment during acute illness.
3. **Gestational diabetes.**
4. **Other specific types** (e.g., pancreatectomy, genetic β-cell defects, defective insulin action).
5. **Drug- or chemical-induced** (e.g., catecholamines, glucocorticoids).

III. DIAGNOSIS

A. Hyperglycemia is defined as a fasting blood glucose above 126 mg/dL, or any random blood glucose >200 mg/dL.

B. Treatment is recommended for blood glucose persistently above 140 to 180 mg/dL.

C. Assess severity.

1. Is ketoacidosis present?
   a. Based upon history, physical findings, and laboratory results (anion gap acidosis and ketonuria or ketonemia).
   b. For management, see Chapter 83.
2. Is hyperosmolarity present?
   a. Based upon extreme hyperglycemia and hyperosmolarity with severe dehydration and obtundation.
   b. For management, see Chapter 83.
3. Is the patient absolutely insulin dependent? Patients with T1D, surgical pancreatectomy, and certain other pancreatic diseases require *continuous insulin tre*atment to avoid ketoacidosis.

D. Evaluation of the ICU patient with preexisting diabetes.

1. Assess cardiac function and peripheral circulation.
2. Look for the following:
   a. Occult infections (e.g., osteomyelitis, cellulitis, cholecystitis, gingivitis, sinusitis, cystitis, or pyelonephritis).
   b. Hypertriglyceridemia as it may cause pancreatitis.
   c. Diabetic eye disease: though it does *not* contraindicate anticoagulation, its severity should be documented before instituting anticoagulation.
   d. Autonomic neuropathy may predispose to orthostasis, tachyarrhythmias, and intestinal dysmotility; should be suspected based upon the EKG (absence of R-R interval changes).
3. Kidney function assessment should include testing for proteinuria.
4. Poorly controlled diabetes may imply poor nutrition or thiamine deficiency.

E. Bedside blood glucose monitoring.

1. Can be influenced by hematocrit, serum creatinine, and arterial Po_2.
2. Less accurate at blood glucose extremes, so should be verified with a sample sent to the laboratory.
3. Do *not* delay therapy awaiting confirmatory laboratory results.

IV. TREATMENT

A. Target blood glucose concentration.

1. While there is a general agreement that excessive hyperglycemia in the ICU should be controlled, specific glycemia control targets remain controversial.
2. One center's early surgical ICU studies suggested that intensive insulin therapy with a target plasma glucose concentration ≤110 mg/dL reduced in-hospital mortality and morbidity, but several subsequent randomized controlled trials in various ICU settings have not documented comparable benefit.
3. NICE-SUGAR, the largest trial to date, demonstrated that the intensive treatment group targeting blood glucose levels between 81 and 108 mg/dL had significantly more hypoglycemia and increased mortality.
4. A 2009 consensus statement from the American Association of Clinical Endocrinologists and American Diabetes Association endorsed good blood glucose control, targeting ICU blood glucose levels between 140 and 180 mg/dL. The Society of Critical Care Medicine recommends a target range of 100 to 150 mg/dL.
5. We suggest the following guidelines for ICU hyperglycemia management:
   a. All critically ill or surgical patients with a plasma glucose concentration ≥180 mg/dL be treated to lower that concentration.
   b. Maintain plasma glucose as close to the normal range as is safely possible, targeting 100 to 180 mg/dL.
   c. Certain patient groups may benefit from tighter control, and this needs to be individualized.
   d. Initial management should be with intravenous insulin infusion therapy.
   e. Avoid glucose concentrations ≤80 mg/dL because they pose the hazard of hypoglycemia and may contribute to mortality.

B. Initiating intravenous insulin infusion.

1. Begin insulin infusion if two consecutive glucose values are >140 to 180 mg/dL, based on institutional protocols or published intravenous insulin protocols.
2. Insulin requirements may be influenced by the primary illness, its treatment, and the patient's body mass index.

C. Adjusting the insulin infusion rate.

1. Institutions are advised to implement an algorithm to achieve target blood glucose concentrations of 100 to 180 mg/dL. Various institutions have published protocols that can be accessed via the Internet.
2. The regular insulin infusion is based on *both* the glucose concentration absolute value *and* its rate of change.
3. Glucose concentrations are checked hourly until in the target range for two consecutive readings and every 2 hours thereafter.
4. Special considerations.
   a. Decrease exogenous carbohydrate loads prior to increasing insulin above 20 units/hour.
   b. Hepatic failure, renal failure, or adrenal insufficiency can lead to a decreased insulin requirement.
   c. A continuous glucose source is strongly recommended for all patients when glucose is <200 mg/dL.

D. Transitioning to subcutaneous insulin.

1. Criteria for transitioning.
   a. Clinical condition has stabilized.
   b. For the previous 6 hours, the patient's intravenous insulin dose has been stable and their glucose has been within the target range.
   c. Caloric intake has remained stable over the past 24 hours.
   d. Corticosteroid dose is not changing.
2. Calculate insulin requirement.
   a. Institutions are advised to adopt a protocol to transition from intravenous to subcutaneous insulin regimens.
   b. Establish 24-hour insulin requirement, extrapolating from the average over the last 4 to 8 hours if stable.
   c. Give 50% as basal insulin and plan 50% as bolus/prandial insulin. Adjust the prandial insulin based on food intake. A correction bolus can be added for blood sugar levels above 150.
   d. Intravenous regular insulin *should be continued* for 2 to 3 hours after the first subcutaneous insulin is injected, since absorption can be delayed.

E. Oral agents and sliding scale insulin in the ICU.

1. Oral hypoglycemic agents should *not be used* in the ICU.
   a. Metformin (Glucophage) due to risk of lactic acidosis.
   b. Thiazolidinediones (Actos) due to risk of congestive heart failure.
2. Sliding scale insulin should also be avoided in the ICU, since it amplifies the risk for both hypoglycemia and hyperglycemia. Rather, the goal is to prevent both hyper- and hypoglycemia.

V. SPECIAL CONSIDERATIONS

A. Surgery in the critically ill patient with diabetes.

1. Patients in the emergency department with hyperglycemia and being prepared for urgent surgery can be treated with either subcutaneous short-acting insulin or, preferably, a continuous insulin infusion.
2. Critically ill patients with hyperglycemia should be treated with an insulin infusion during surgery.
3. Anesthetic agents may exacerbate hyperglycemia. Regional and local anesthetics are preferable when appropriate.

B. Hyperalimentation and hyperglycemia.

1. Insulin added to parenteral nutrition formulations should be limited to ≤50% of the patient's anticipated total insulin requirement for the duration of the feeding.
2. Additional insulin should be administered by intravenous infusion or subcutaneous injection.
3. If a patient receiving total parenteral nutrition develops severe hyperglycemia and a large insulin requirement, consideration should be given to reducing the carbohydrates administered.

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83 Diabetic Comas: Ketoacidosis and Hyperosmolar Syndrome

Samir Malkani and John P. Mordes

I. GENERAL PRINCIPLES

A. The four conditions related to severely disordered glucose metabolism and often associated with altered consciousness and coma are the following:

1. Diabetic ketoacidosis (DKA).
2. Hyperglycemic hyperosmolar syndrome (HHS).
3. Alcoholic ketoacidosis.
4. Hypoglycemia.

B. These four diagnoses should be considered during the evaluation of any patient with altered mental status.

II. DIABETIC KETOACIDOSIS

A. Etiology.

1. DKA may be the first sign of new-onset type 1 diabetes mellitus but more commonly occurs in those with preexisting type 1 diabetes due to the following:
   - **a.** Omission of insulin therapy.
   - **b.** Infection.
   - **c.** Major stressors (e.g., myocardial infarction, trauma).
   - **d.** Medication (e.g., high-dose glucocorticoid therapy).
2. DKA occurs less commonly in patients with type 2 diabetes in the presence of severe infection, trauma, or myocardial infarction. Among individuals with type 2 diabetes, African Americans and ethnic minorities seem to be more prone to DKA than Caucasians.

B. Pathophysiology.

1. Caused by a total or near-total absence of circulating insulin, coupled with increased secretion of glucagon.
2. These hormonal changes are responsible for the following:
   - **a.** Inability of glucose to enter cells and unrestrained hepatic glucose production leading to severe hyperglycemia.
   - **b.** Acceleration of lipolysis and release of large quantities of free fatty acids, which are metabolized to ketone bodies.
3. The large amounts of ketones generated result in the accumulation of hydrogen ions and metabolic acidosis.

4. Hyperglycemia causes an osmotic diuresis resulting in a loss of free water and depletion of electrolytes.
5. Other stress hormones such as cortisol facilitate the above changes in glucose and lipid metabolism.

C. Diagnosis.

1. Clinical manifestations.
   a. Most patients with DKA are lethargic; approximately 10% are comatose.
   b. Postural hypotension is common, but shock is rare.
   c. There is a rapid, deep (Kussmaul) respiration, and a sweet, fruity odor in the breath.
   d. Presence of fever should alert to the presence of an intercurrent illness. Hypothermia may be a sign of sepsis.
   e. Abdominal pain and nausea are common and may be accompanied by guarding and diminished bowel sounds. Patients may vomit guaiac-positive, coffee ground–like material.
   f. Pleuritic chest pain may be present. Hepatic enlargement with fatty infiltration may occur.
2. Laboratory.
   a. Plasma glucose is typically in the range of 250 to 800 mg/dL in DKA.
   b. Electrolytes.
      i. Serum sodium concentration can vary from 125 to 165 mEq/L. It usually decreases due to osmotic diuresis and dilution by the osmotic effect of hyperglycemia. For every 100 mg increase in glucose the dilutional effect accounts for a 1.6-mEq/L drop in sodium concentration.
         (a) Example: The "corrected" serum sodium in a patient with a measured concentration of 135 mEq/L and a glucose of 600 mg/dL is $1.6 \times (600 - 100) + 135$, or 143 mEq/L. Hypertriglyceridemia can cause a factitiously low sodium concentration.
      ii. Potassium concentration is usually elevated at presentation but can vary from 2.2 to 8.4 mEq/L. It can drop during treatment to the point of being life threatening.
         (a) A total body potassium deficit in the range of 200 to 700 mEq is typical even when the potassium is moderately elevated.
         (b) A normal or low concentration of potassium at presentation often signals a very severe potassium deficit.
      iii. Phosphorus concentrations are commonly elevated in untreated DKA. After therapy, there is a precipitous decline to subnormal levels.
   c. Anion gap acidosis is seen at presentation.
      i. Arterial pH measurements are preferred, but venous pH may also be used.
      ii. Chronic ketoacidotic states may be associated with hyperchloremic acidosis, probably as a consequence of the loss of neutralized ketone body salts.
      iii. Rarely, metabolic alkalosis is observed from severe vomiting.

d. Plasma ketone levels by the nitroprusside test may not reflect the full extent of ketogenesis, and direct β-hydroxybutyrate (BOHB) measurements may be more helpful in establishing the diagnosis and assessing severity.
  i. The nitroprusside test measures only acetoacetate (AcAc) and acetone. BOHB, the predominant "ketone body" produced from AcAc, is not measured by this test.
  ii. Normally, the BOHB:AcAc ratio is 3:1, but acidosis increases the ratio to 6:1 or even 12:1.
  iii. Ketone measurements by nitroprusside may initially rise due to conversion of BOHB back to AcAc as acidosis resolves. Clearance occurs slowly; measurement more often than every 12 hours is generally unnecessary.

e. A mixed anion gap acidosis may occur in patients with DKA. This can be due, for example, to intercurrent lactic acidosis or salicylate intoxication.
  i. If the total ketoacid concentration (the sum of BOHB and estimated AcAc concentrations) is much lower than the increase in anion gap, a non–ketone body anion may be contributing to this difference (e.g., lactate, salicylate, uremic compounds, methanol, ethylene glycol).
  ii. Direct measurement of these substances may also be helpful (e.g., lactate).

f. Other laboratory findings.
  i. Renal. The blood urea nitrogen (BUN) is typically elevated due to prerenal azotemia and increased ureagenesis. AcAc can interfere with some creatinine assays.
  ii. Hematology. Hematocrit and hemoglobin are usually high. Low values suggest preexisting anemia or acute blood loss. Leukocytosis with a left shift often occurs in the absence of intercurrent illness.
  iii. Lipids. There is usually marked elevation of serum triglyceride concentrations; this reverses with insulin therapy.
  iv. Serum amylase, lipase, and creatine phosphokinase (CPK) are sometimes elevated. Uric acid may be elevated. Ketone bodies interfere with certain transaminase assays.

D. Treatment.

1. Treatment is directed at four main problems: (1) hypovolemia, (2) electrolyte disturbances, (3) insulin, and (4) identification of the precipitating event. Institutional protocols may be helpful to ensure uniformity and efficacy of treatment.

2. Hypovolemia is always present. Fluid and electrolyte therapy takes precedence over insulin therapy; the latter shifts glucose, salt, and water from the extracellular and intravascular compartments to the intracellular space.
  a. The free water deficit ranges between 5 and 11 L, approximately 100 mL/kg.
  b. Initial fluid resuscitation should be with 0.9% saline.

c. Approximately 2 L should be given during the first hour to stabilize blood pressure and establish urine flow.
d. Another liter can usually be given during the next 2 hours.
e. During the first 24 hours, 75% of the estimated free water deficit should be replaced. Urine flow should be maintained at approximately 30 to 60 mL/hour.
f. After the first 2 L, consider changing to 0.45% saline if hypernatremia is present.

3. Electrolytes.
a. Sodium and chloride are replaced in conjunction with free water as described above.
b. The initial serum potassium level does not accurately reflect the total-body potassium deficit. Potassium replacement must always be initiated early in treatment.
i. Potassium replacement should begin as soon as the serum K^+ concentration is ≤5.5 mEq/L, because potassium concentration often falls precipitously after starting therapy. Reasons for this include the following:
(a) Insulin shifts K^+ intracellularly.
(b) As acidemia resolves, buffered intracellular H^+ exchanges for extracellular K^+.
(c) Gastric suctioning via a nasogastric tube may result in the loss of electrolytes.
ii. A sudden reduction in the serum potassium concentration can cause flaccid paralysis, respiratory failure, and life-threatening cardiac arrhythmias.
iii. The typical rate of repletion is 20 mEq/hour as KCl or K_3PO_4; in severe hypokalemia 40 mEq/hour may be required.
iv. Potassium deficits in DKA are 3 to 5 mEq/kg, but if hypokalemia or normokalemia is present at admission, the deficit may be up to 10 mEq/kg.
v. In mild DKA where the patient is alert and able to tolerate liquids, potassium should be given orally.
c. Phosphate concentration is elevated initially, but levels may decrease to <1 mM/L within 4 to 6 hours of starting insulin treatment.
i. Severe hypophosphatemia can cause neurologic disturbances, arthralgias, muscle weakness with respiratory failure, rhabdomyolysis, and liver dysfunction.
ii. 5 mL (one ampule) of potassium phosphate may be administered in severe hypophosphatemia (<1.0 mg/dL). This solution contains 93 mg phosphorus and 4 mEq potassium/mL.
iii. Complications of parenteral phosphate administration include hypocalcemia and metastatic calcification.
d. Bicarbonate use is not generally recommended during treatment of DKA.
i. Bicarbonate administration can be associated with severe hypokalemia, late respiratory alkalosis due to paradoxical cerebrospinal fluid acidosis, a shift of the oxygen dissociation curve to the left

(causing tissue hypoxia and lactic acidosis), increased hepatic ketogenesis, and increased risk of cerebral edema in children.

ii. Fluid and electrolyte replacement alone will ameliorate acidosis.

iii. Bicarbonate therapy may be appropriate in those with a pH ≤ 7.0 who have associated respiratory depression or severe hypotension unresponsive to aggressive fluid replacement.

iv. When required, sodium bicarbonate is added to intravenous fluids, typically two ampules (2 × 44 mEq, or 2 × 50 mEq) added to 1 L of D5W. When the pH is ≥7.1, treatment should be stopped.

e. Magnesium concentration may be high early in the course of DKA. It generally returns to normal without treatment. In some patients, Mg^{2+} stores may be depleted and in rare instances lead to cardiac arrhythmia.

4. Insulin therapy in DKA should be instituted *only* after fluid and electrolyte resuscitation is under way.

a. For adults, give a bolus of 10 units of short-acting insulin followed by a continuous intravenous infusion starting at 5 to 10 units/hour.

b. In children, the recommended initial bolus is 0.1 units/kg of body weight and the infusion rate is 0.1 units/kg/h.

c. Insulin should be added to 0.45% or 0.9% saline at a concentration of 0.5 or 1.0 units/mL, and the container swirled before use. To avoid error, insulin concentration for intravenous infusion should be standardized within each hospital.

d. Either regular or semisynthetic rapid-acting insulin can be used.

e. Plasma glucose should be measured every 1 to 2 hours after starting the infusion.

i. If the glucose concentration has not decreased by 100 mg/dL, the insulin infusion rate should be doubled.

ii. When the glucose concentration has fallen by >150 mg/dL, the infusion rate should be decreased by 50%, but it should never be stopped.

iii. The minimum plasma glucose concentration during the first 24 hours of treatment should be 200 mg/dL.

iv. If plasma glucose falls below 200 mg/dL, glucose infusion (dextrose 5% in water [D5W]) should be started, and the insulin infusion continued to inhibit ketogenesis. *Never* stop insulin entirely during the treatment of DKA, even if the rate is reduced to only 0.5 units/hour.

f. Serum bicarbonate levels should be near normal before transitioning the patient from intravenous insulin to subcutaneous insulin injections.

g. Insulin infusion should only be stopped 2 to 3 hours after the first dose of subcutaneous insulin.

h. In mild DKA repeated doses of subcutaneous rapid-acting insulin have been used successfully.

5. Identification of the precipitating event.

a. Precipitating cause such as missing insulin, infection, trauma, or a medication predisposing to DKA can be identified in only 50% of the patients, but should always be looked for.

b. If the precipitating cause is left untreated, DKA may recur.

E. Complications.

1. Hypokalemia.
2. Recurrence of DKA during the hospital stay.
   a. Stopping insulin early is the commonest cause for recurrence. Correction of glucose is not the end point for treatment, and insulin infusion should be continued until acidemia resolves, and the patient is well enough to be switched to subcutaneous injections of insulin.
   b. If ketoacidosis recurs despite continued therapy with insulin, severe infection, a severe contrainsulin state (e.g., Cushing syndrome), or medications (e.g., glucocorticoids) should be suspected.
3. Cerebral edema is a rare complication of DKA in adults, but it occurs occasionally in children.
   a. To reduce the risk of cerebral edema, the plasma glucose concentration should not be allowed to fall below 200 mg/dL during the first 24 hours.
   b. Rapid fall in corrected sodium may also be associated with cerebral edema.
4. Persistent hypotension can occur from fluid shifts when glucose drops too rapidly, bleeding, severe acidosis, arrhythmia, myocardial infarction, cardiac tamponade, sepsis, and adrenal insufficiency.
5. Renal complications include postrenal obstruction, atonic bladder, and acute tubular necrosis secondary to pyelonephritis.
6. Thrombosis of cerebral vessels and stroke are uncommon complications.
7. Hyperchloremic metabolic acidosis with normal anion gap frequently develops after therapy and corrects spontaneously.

III. HYPERGLYCEMIC HYPEROSMOLAR SYNDROME

A. Etiology.

Progressive unrecognized advanced hyperglycemia occurring in individuals with type 2 diabetes leading to severe dehydration, electrolyte imbalance, and altered mental status.

B. Pathophysiology.

The pathophysiology of HHS involves three interrelated elements:

1. Insulin deficiency.
   a. Patients have relative insulin deficiency—there is enough insulin to inhibit ketone body formation but not enough to prevent glycogenolysis and gluconeogenesis.
   b. The resulting hyperglycemia induces an osmotic diuresis, with resultant fluid and electrolyte losses.
2. Renal impairment.
   a. There is some degree of renal impairment such that affected patients are unable to compensate for the hyperglycemia with an osmotic diuresis.
   b. Typical patients with HHS are older and have reduced renal blood flow and glomerular filtration rate (GFR).
   c. The underlying abnormalities in HHS may be prerenal, renal, or postrenal.

3. Cognitive impairment.
   a. HHS involves acute or chronic impairment of cerebral function.
   b. There is a failure of the thirst mechanism normally activated by the osmotic diuresis resulting from hyperglycemia, which results in progressive dehydration.
   c. Individuals with cognitive impairment due to cerebrovascular disease, dementia, or central nervous system (CNS)-depressant medications and patients with trauma or burns are susceptible to HHS.

C. Diagnosis.

1. Clinical presentation.
   a. Occurs typically in middle-aged or elderly individuals who often have a history of type 2 diabetes or glucose intolerance and a prodrome of progressive polyuria and polydipsia lasting days to weeks. There are a few recent reports of HHS occurring in children and young adults.
   b. Most patients have intercurrent illnesses; renal and cardiovascular disorders are common.
   c. Other predisposing problems include infection, myocardial infarction, stroke, hemorrhage, and trauma. Additional factors include dialysis, hyperalimentation, and medications (e.g., thiazide diuretics, antipsychotics, phenytoin, propranolol, immunosuppressive agents, and diazoxide).
   d. Fever is a common finding in HHS even in the absence of infection. Infection must be rigorously excluded in all cases.
   e. Hypotension and tachycardia occur due to dehydration.
   f. Hyperventilation may reflect intercurrent lactic acidosis.
   g. Neurologic manifestations include tremors and fasciculations. Mental status abnormalities range from mild disorientation to obtundation and coma. Seizures occur in upto 30% individuals.

2. Laboratory.
   a. Plasma glucose concentrations in HHS are generally higher than in DKA, usually >600 mg/dL. Values as high as 2,000 mg/dL occur.
   b. Serum ketones are usually normal or only slightly elevated.
   c. Arterial pH averages about 7.25. Occasional patients will develop a mild metabolic acidosis.
   d. Serum osmolality in comatose patients usually exceeds 350 mOsm/kg.
   e. Prerenal azotemia is induced by dehydration.
   f. Serum sodium at presentation is variable, ranging between 100 and 180 mEq/L. "Corrected" serum sodium concentration is calculated as for DKA.
   g. Serum potassium concentration is also variable, in our experience from 2.2 to 7.8 mEq/L.

D. Treatment.

Treatment of HHS should be directed at four main problems: (1) hypovolemia, (2) electrolyte disturbances, (3) insulin, and (4) identification of the precipitating event.

1. Correction of hypovolemia.
   a. Patients with HHS are profoundly dehydrated. Fluid deficit is between 100 and 200 mL/kg.
   b. Within the first 2 hours, 1 to 2 L of 0.9% saline should be given.
   c. Normal saline is recommended, even in the presence of hypernatremia, to expand the extracellular fluid compartment rapidly.
   d. After initial volume expansion and restoration of normotension, subsequent replacement emphasizes free water.
   e. The average patient requires 6 to 8 L of fluids during the first 12 hours. Hemodynamic monitoring is advised during aggressive rehydration in the elderly person with heart disease.
2. Electrolytes.
   a. Potassium replacement should be started as soon as urine flow has been established and the degree of hypokalemia estimated.
   b. A rapid fall in the serum potassium concentration frequently accompanies insulin therapy.
   c. Serum potassium should be checked frequently and the electrocardiogram monitored.
   d. Cardiac arrhythmias induced by hypokalemia may be irreversible, particularly in the elderly.
3. Insulin.
   a. Most patients with HHS are more sensitive to insulin than are patients with DKA.
   b. Blood glucose concentration can fall precipitously when urine output is reestablished after volume expansion.
   c. Insulin treatment should be instituted only after fluid and electrolyte resuscitation is under way. Insulin infusion should be started at 1 to 5 units/hour, depending on individual circumstances, with careful monitoring. An initial bolus is not recommended.
   d. Attempt to maintain blood glucose concentration near 250 mg/dL for the first 24 hours. A rapid fall in blood glucose concentration causes rapid osmotic shifts, and can predispose to hypotension and cerebral edema.
4. Identification of the precipitating event.
   a. The underlying cause for HHS should always be sought.
   b. Common precipitating events include infection and major stressors (e.g., myocardial infarction or trauma).
   c. Less common are drugs that depress the sensorium and inhibit the response to thirst (e.g., anxiolytics and sedatives), drugs that depress renal function (e.g., diuretics leading to prerenal azotemia), and drugs that promote hyperglycemia (e.g., steroids) and other endocrine disturbances (e.g., hypothyroidism or apathetic thyrotoxicosis).

E. Complications.

1. Mortality rates of 15% have been reported in type 1 diabetics.
2. Arterial thrombosis can lead to stroke and myocardial infarction.
3. Rhabdomyolysis.
4. Cerebral edema.

IV. ALCOHOLIC KETOACIDOSIS

A. Pathophysiology.

1. Ingestion of a large quantity of ethanol interferes with gluconeogenesis (but not glycogenolysis) via several mechanisms.
2. Hypoglycemia ensues when glycogen stores are exhausted, explaining the relationship of the disorder to the nutritional state.
3. Hypoglycemia lowers insulin levels, which then permits release of free fatty acids from adipose tissue and formation of ketone bodies.

B. Diagnosis.

1. Ketoacidosis in the presence of hypoglycemia.
2. A history of significant alcohol intake may be available.
3. Definitive diagnosis of hypoglycemia has three components: low plasma glucose concentration, neuroglycopenic symptoms (e.g., hunger, headache, confusion, lethargy, slurred speech, seizures, coma) consistent with hypoglycemia, and resolution of those symptoms with administration of glucose.

C. Clinical presentation.

1. Occurs typically in alcohol abusers but can occur after binge drinking in adults or accidental ingestion in children.
2. Adult patients typically have not eaten for days and are prone to nausea, vomiting, and aspiration.
3. Patients may be stuporous or comatose. Hypothermia and neurologic abnormalities, including trismus, seizures, hemiparesis, and abnormal tendon reflexes, may be observed.
4. Evidence of inebriation is often absent.

D. Laboratory.

1. Hypoglycemia: Blood glucose concentrations can be as low as 20 mg/dL.
2. Anion gap acidosis: These patients are usually acidotic, with an arterial pH < 7.2.
3. Both ketoacids and lactate contribute to the unmeasured anion pool in this form of acidosis. The presence of ketoacids in a hypoglycemic patient excludes hyperinsulinemia as the cause of hypoglycemia.
4. By the time patients with this disorder are treated, the ethanol has often been metabolized and is no longer detectable.
5. Liver function tests, amylase, and phosphate are typically normal.

E. Treatment.

1. Fluids and electrolytes: Rehydration with intravenous fluids as appropriate.
2. Glucose.
   a. One ampule of dextrose 50% in water (D50W) to correct hypoglycemia, being careful to avoid extravasation.
   b. Treatment with glucose and fluids rapidly reverses the condition by raising the concentration of insulin and thereby inhibiting lipolysis and free fatty acid release.
3. Parenteral thiamine (100 mg) to prevent Wernicke encephalopathy.

V. HYPOGLYCEMIC COMA

Hypoglycemic emergencies are discussed in Chapter 87.

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84 Thyroid Disorders in the ICU

Alan P. Farwell

I. THYROID STORM

A. General principles.

1. Thyroid storm is a rare, life-threatening complication of thyrotoxicosis in which a severe form of the disease is usually precipitated by an intercurrent medical problem.
2. Thyroid storm is primarily a clinical diagnosis, as there are no absolute levels of elevated thyroid hormones that are diagnostic of storm.
3. Thyroid storm is a medical emergency that should be managed in the ICU.

B. Etiology.

1. Hyperthyroidism is the most common cause of thyrotoxicosis leading to thyroid storm.
2. Precipitating factors associated with thyroid storm include infections, stress, trauma, thyroidal or nonthyroidal surgery, diabetic ketoacidosis, labor, heart disease, iodinated contrast studies, thyroid hormone overdose, and radioiodine treatment (especially if there was no pretreatment with antithyroid drugs).
3. Historically, thyroid storm was frequently associated with surgery for hyperthyroidism, but this is rarely seen now.

C. Pathophysiology.

1. Thyroid storm is the most severe manifestation of thyrotoxicosis, and the onset is rapid.
2. Increased levels of T4 and T3 are necessary, but there is no absolute level that establishes the diagnosis.
3. While the cause of the rapid clinical decompensation is unknown, a sudden inhibition of thyroid hormone binding to plasma proteins by the precipitating factor, causing a rise in free hormone concentrations in the already elevated free hormone pool, may play a role in the pathogenesis of thyroid storm.

D. Diagnosis.

1. **Symptoms.**
   a. Thyroid storm is primarily a clinical diagnosis, with features similar to those of thyrotoxicosis, but more exaggerated (Table 84-1).
   b. Cardinal features include fever (temperature usually >38.5°C), tachycardia out of proportion to the fever, and mental status changes.

TABLE 84-1 Clinical Features of Thyroid Storm

Fever (as high as 105.8°F)
Tachycardia/tachyarrhythmias
Delerium/agitation
Mental status changes
Congestive heart failure
Tremor
Nausea and vomiting
Diarrhea
Sweating
Vasodilatation
Dehydration
Hepatomegly
Splenomegly
Jaundice

c. Tachyarrhythmias, especially atrial fibrillation in the elderly, are common, as are nausea, vomiting, diarrhea, agitation, and delirium.

d. Coma and death may ensue in up to 20% of patients, frequently due to cardiac arrhythmias, congestive heart failure (CHF), hyperthermia, or the precipitating illness.

2. Signs.

a. Most patients display the classic signs of Graves disease, including ophthalmopathy and a diffusely enlarged goiter, although thyroid storm has been associated with toxic nodular goiters.

b. In the elderly, severe myopathy, profound weight loss, apathy, and a minimally enlarged goiter may be observed.

c. There are no distinct laboratory abnormalities, and thyroid hormone levels are similar to those found in uncomplicated thyrotoxicosis; there is little correlation between the degree of elevation of thyroid hormones and the presentation of thyroid storm.

3. Differential diagnosis.

a. The differential diagnosis of thyroid storm includes sepsis, neuroleptic malignant syndrome, malignant hyperthermia, and acute mania with lethal catatonia, all of which can precipitate thyroid storm in the appropriate setting.

b. Clues to the diagnosis of thyroid storm are a history of thyroid disease, history of iodine ingestion, and the presence of a goiter or stigmata of Graves disease.

c. Burch and Wartofsky have published a scoring system for the diagnosis of thyroid storm (Table 84-2). The diagnosis of thyroid storm was possible with a score of 25 to 45 and is likely with a score >45. Thyroid storm is unlikely with a score <25.

TABLE 84-2 Clinical Scoring System for the Diagnosis of Thyroid Storm (Burch and Wartofsky)

	Score
Temperature (°F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
>104	30
CNS effects	
Absent	0
Mild agitation	10
Moderate	20
Severe	30
Precipitant history	
None	0
Present	10
GI–hepatic	
Absent	0
Moderate	10
Severe (Jaundice)	20
Pulse	
90–09	5
110–119	10
120–129	15
130–139	20
>140	25
CHF	
Absent	0
Mild	5
Moderate	10
Severe	15
AFib	
Absent	0
Present	10

d. A recent study suggested new criteria for the rapid diagnosis of thyroid storm.

i. Patients who had specific CNS manifestations (restlessness, delirium, psychosis/mental aberrations, somnolence/lethargy, convulsions) needed to have only one of four additional conditions: temperature

of 38°C or higher; tachycardia of 130 beats per minute or higher; class IV CHF; or gastrointestinal/hepatic manifestations (diarrhea, nausea/vomiting, or a bilirubin above 3 mg/dL).

ii. Those without CNS mainfestations needed three out of four conditions: temperature of 38°C or higher; tachycardia of 130 beats per minute or higher; class IV CHF; or gastrointestinal (GI)/hepatic manifestations (diarrhea, nausea/vomiting, or a bilirubin above 3 mg/dL).

e. In any event, the physician must have a high clinical index of suspicion for thyroid storm, as therapy must be instituted before the return of thyroid function tests in most cases.

E. Treatment.

1. Thyroid storm is a major medical emergency that must be treated in an ICU (Table 84-3).
2. Treatment includes supportive measures such as intravenous fluids, antipyretics, cooling blankets, and sedation.
3. β-Adrenergic blockers or calcium channel blockers are given to control tachyarrhythmias.
4. Antithyroid drugs are given in large doses, with propylthiouracil (PTU) being preferred over methimazole due to its additional advantage of impairing peripheral conversion of T4 to T3.
5. PTU and methimazole can be administered by nasogastric tube or rectally if necessary; neither of these preparations is available for parenteral administration.
6. Iodides, orally or intravenously, may be used only after antithyroid drugs have been administered, although the useful radiographic contrast dye iopanoic acid is no longer available in the United States.
7. High-dose dexamethasone is recommended as supportive therapy, as an inhibitor of T4-to-T3 conversion and as management of possible intercurrent adrenal insufficiency.
8. Orally administered ion-exchange resins (colestipol or cholestyramine) can trap hormone in the intestine and prevent recirculation, and plasmapheresis has also been used in severe cases.
9. Treatment of the underlying precipitating illness is essential to survival in thyroid storm.
10. Once stabilized, the antithyroid treatment should be continued until euthyroidism is achieved, at which point a final decision regarding antithyroid drugs, surgery, or ^{131}Iodine (^{131}I) therapy can be made.

F. Complications.

1. The mortality rate of thyroid storm has been reported to be 10% to 20%.
2. Complications of thyroid storm other than mortality are the same as complications from the underlying etiology of the thyrotoxicosis (i.e., opthalmopathy in Graves disease).
3. After definitive therapy for hyperthyroidism (surgery or radioactive iodine), hypothyroidism is the most common, and desired, result.

TABLE 84-3 Treatment of Thyroid Storm

Supportive therapy
Treatment of underlying illnesses
Intravenous fluids
Cooling blanket and/or antipyretics

β–Adrenergic blocking drugs
Propranolol—1 mg IV/min to a total dose of 10 mg, then 40–80 mg PO q6 h, *or*
Esmolol—500 mg/kg/min IV, then 50–100 mg/kg/min, *or*
Metoprolol—100–400 mg PO q12 h, *or*
Atenolol—50–100 mg PO daily

Antithyroid drugs
Inhibition of thyroid hormone synthesis
PTU—800 mg PO first dose, then 200–300 mg PO q8 h, *or*
Methimazole—80 mg PO first dose, then 40–80 mg PO q12 h

Block release of thyroid hormones from the gland
SSKI—5 drops PO q8 h, *or*
Lugol solution—10 drops PO q8 h, *or*
Lithium—800–1,200 mg PO qd—achieve serum lithium levels 0.5–1.5 mEq/L

Block T4-to-T3 conversion
Corticosteroids—dexamethasone 1–2 mg PO q6 h
Most β-blockers—propranolol 40–80 mg PO q6 h
Propylthiouracil
Telapaque (iopanoic acid)—no longer available in the United States

Remove thyroid hormones from the circulation
Plasmapheresis, *or*
Peritoneal dialysis, *or*
Cholestyramine—4 g PO q6 h, *or*
Colestipol—20–30 mg PO qd

SSKI, saturated solution of potassium iodide.

II. MYXEDEMA COMA

A. General principles.

1. Myxedema coma is a rare syndrome that represents the extreme expression of severe, long-standing hypothyroidism.
2. Even with early diagnosis and treatment, the mortality can be as high as 60%.
3. Myxedema coma occurs most often in the elderly and during the late fall and winter months.
4. Myxedema coma is primarily a clinical diagnosis, as there are no absolute levels of decreased thyroid hormones that are diagnostic.
5. Myxedema coma is a medical emergency that should be managed in the ICU.

B. Etiology.

1. Hypothyroidism by any cause can be the underlying cause of myxedema coma.
2. Most episoides of myxedema coma are caused by a precipitating factor in the setting of severe hypothyroidism.
3. Common precipitating factors include pulmonary infections, cerebrovascular accidents, trauma, surgery, and CHF.
4. The clinical course of lethargy proceeding to stupor and then coma is often hastened by drugs, especially sedatives, narcotics, antidepressants, and tranquilizers, especially in the undiagnosed hypothyroid patient who has been hospitalized for other medical problems.

C. Pathophysiology.

1. Myxedma coma is the most severe manifestation of hypothyroidsm.
2. Decreased levels of T4 and T3 and increases in thyroid-stimulating hormone (TSH) are necessary, but there is no absolute level upon which the diagnosis is clear.

D. Diagnosis.

1. **Symptoms.**
   - **a.** Cardinal features of myxedema coma are hypothermia, respiratory depression, hypotension, and unconsciousness (Table 84-4).
   - **b.** Most patients have the physical features of severe hypothyroidism, including bradycardia; macroglossia; delayed reflexes; and dry, rough skin and myxedematous facies, which result from the periorbital edema, pallor, hypercarotinemia, periorbital edema, and patchy hair loss.
   - **c.** Hypotonia of the gastrointestinal tract is common and often so severe as to suggest an obstructive lesion.
   - **d.** Urinary retention due to a hypotonic bladder is related but less frequent.

TABLE 84-4 Clinical Features of Myxedema Coma

Mental obtundation
Hypothermia
Bradycardia
Hypotension
Coarse, dry skin
Myxedema facies
Hypoglycemia
Atonic GI tract
Atonic bladder
Pleural, pericardial, and peritoneal effusions

GI, gastrointestinal.

2. **Signs.**
   a. Pleural, pericardial, and peritoneal effusions may be present.
   b. The thyroid hormone abnormalities are similar to those in uncomplicated hypothyroidism, with >95% of cases due to primary hypothyroidism.
   c. Dilutional hyponatremia is common and may be severe.
   d. Elevated creatine kinase concentrations, sometimes markedly so, are encountered frequently, suggesting cardiac ischemia; however, in most cases the myocardial band (MB) fraction is normal, and an electrocardiogram (ECG) often shows the low voltage and loss of T waves that are characteristic of severe hypothyroidism.
   e. Elevated lactate dehydrogenase concentrations, acidosis, and anemia are common findings.
   f. Lumbar puncture reveals increased opening pressure and high protein content.
3. **Differential diagnosis.**
   a. The diagnosis of myxedema coma is based on the presence of the characteristic clinical syndrome in a patient with hypothyroidism.
   b. Clues to the diagnosis include symptoms related by family and friends, an outdated container of L-T4 discovered with the patient's belongings, previous treatment with radioactive iodine, or there may be a thyroidectomy scar present.
   c. Differential diagnosis includes protein-calorie malnutrition, sepsis, hypoglycemia, exposure to certain drugs and toxins, and cold exposure.
   d. What distinguishes myxedema coma from other disorders is the combination of laboratory evidence of hypothyroidism, the characteristic myxedema facies with periorbital puffiness, the skin changes, obtundation, and other physical signs characteristic of severe hypothyroidism.
   e. The physician must have a high clinical index of suspicion for myxedema coma, as therapy must be instituted before the return of thyroid function tests in most cases.

E. Treatment.

1. Myxedema is a medical emergency and must be managed in an ICU setting (Table 84-5).
2. The mainstays of therapy are supportive care, with ventilatory and hemodynamic support, rewarming, correction of hyponatremia and hypoglycemia, and treatment of the precipitating incident and administration of thyroid hormone.
3. Active heating in myxedema coma should be avoided as it increases oxygen consumption and promotes peripheral vasodilation and circulatory collapse.
   a. An exception is at core temperatures below 28°C, when ventricular fibrillation is a major threat to life—in this case, the rate of rewarming should not exceed 0.5°C/hour until the core temperature is raised to approximately 31°C.
   b. In general, patients should be kept in a warm room and covered with blankets.

TABLE 84-5 Treatment of Myxedema Coma

Assisted ventilation for hypoventilation
Hemodynamic support for hypotension
Intravenous glucose for hypoglycemia
Water restriction or hypertonic saline for severe hyponatremia
Passive rewarming for hypothermia
Administer thyroid hormone intravenously
  L-T4—200–300 μg loading dose, up to 500 μg in the first 24 h[a] and/or
  L-T3—12.5 μg q6 h until awake[a]
  Administer hydrocortisone IV (100 mg q8 h)[a]
  Treat underlying infection and other illnesses, if present
  Avoid all sedatives, hypnotics, and narcotics

[a]Note that dosage must be individualized (see text).

4. Sedatives, hypnotics, narcotics, and anesthetics must be minimized or avoided altogether due to their extended duration of action and exacerbation of obtundation in the hypothyroid patient.
5. Because of a 5% to 10% incidence of coexisting adrenal insufficiency in patients with myxedema coma, intravenous steroids are indicated before initiating T4 therapy.
6. Parenteral administration of thyroid hormone is necessary due to uncertain absorption through the gut.
   a. A reasonable approach is an initial intravenous loading dose of 200 to 300 μg L-T4, with another dose of L-T4 given in 6 to 12 hours to bring the total dose during the first 24 hours to 0.5 mg, followed by 50 to 100 μg intravenously every 24 hours until the patient is stabilized.
   b. In the most severe cases, some clinicians recommend using L-T3 at a dosage of 12.5 to 25 μg intravenously every 6 hours until the patient is stable and conscious, followed by a switch to L-T4.
7. Although myxedema coma is associated with substantial mortality risk, many patients can be saved by judicious therapy aimed at correcting the secondary metabolic disturbances and reversing the hypothyroid state in a sustained but gradual fashion, since an effort to correct hypothyroidism too rapidly may completely negate the beneficial effects of the initial treatment.

F. Complications.

1. Despite optimal treatment, the mortality of myxedema coma can be as high as 60%.
2. Hypotonia of the gastrointestinal tract is often so severe as to suggest an obstructive lesion.
3. Urinary retention due to a hypotonic bladder can also be seen.

III. SICK EUTHYROID SYNDROME IN THE INTENSIVE CARE UNIT

A. General principles.

1. Critical illness causes multiple nonspecific alterations in thyroid hormone concentrations in patients who have no previously diagnosed intrinsic thyroid disease that relates to the severity of the illness.
2. There is an ongoing debate whether such alterations are a physiologic adaptation or a pathologic perturbation. Because to the complexity of many patients with the sick euthyroid syndrome, it is likely that both physiologic and pathologic effects play a role.
3. Despite abnormalities in serum thyroid hormone parameters, there is little evidence that critically ill patients have clinically significant thyroid dysfunction. While some investigators have proposed otherwise, there is no current evidence to support thyroid hormone therapy in the management of the sick euthyroid syndrome.
4. While a wide variety of illnesses tend to result in the same changes in serum thyroid hormones, these changes are rarely isolated and often are associated with alterations in other endocrine systems, such as reductions in serum gonadotropin and sex hormone concentrations and increases in serum adrenocorticotropic hormone (ACTH) and cortisol.
5. The sick euthyroid syndrome should not be viewed as an isolated pathologic event but as part of a coordinated systemic reaction to illness that involves both the immune and endocrine systems.

B. Etiology.

1. While the cause of the alterations in thyroid hormone economy in critical illness is largely unknown, cytokines, such as tumor necrosis factor alpha, interleukin 1, and interleukin 6, have been shown to reproduce many of the features of the sick euthyroid syndrome in both animal and human studies when administered in pharmacologic doses.
2. Whether the sick euthyroid syndrome results from activation of the cytokine network or simply represents an endocrine response to systemic illness resulting from the same mediators that trigger the cytokine cascade remains to be determined.

C. Pathophysiology.

1. **Alterations in peripheral metabolic pathways.**
   - **a.** The major pathway of metabolism of thyroxine (T4) is by sequential monodeiodination by type 1 (D1) or type 2 deiodinase (D2) to generate triiodothyronine (T3) (activating pathway) or type 3 deiodinase (D3) to generate rT3 (inactivating pathway).
   - **b.** One of the first alterations in thyroid hormone metabolism in acute illness is inhibition of D1 in peripheral tissues, which is affected by a wide variety of factors (Table 84-6) and subsequent impairment in T4-to-T3 conversion.
   - **c.** Because >80% of T3 is derived from deiodination of T4 in peripheral tissues, T3 levels fall soon after the onset of acute illness. D1 also deiodinates rT3, so degradation is impaired, and levels of this inactive hormone rise in proportion to the fall in T3 levels.

TABLE 84-6 Factors that Inhibit Thyroxine (T4) to Triiodothyronine (T3) Conversion in Peripheral Tissues

Acute and chronic illness
Caloric deprivation
Malnutrition
Glucocorticoids
β-Adrenergic blocking drugs (e.g., propranalol)
Oral cholecystographic agents (e.g., iopanoic acid[a], sodium ipodate[a])
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency
Cytokines (Il-1, Il-6)

[a]Currently unavailable or limited availability.
Il, interleukin.

d. In general, D3 is unaffected by acute illness, so inner ring deiodination of T4 to produce rT3 is unchanged. However, recent studies have suggested that D3 may be increased in certain tissues, leading to increased T3 disposal within those tissues.

e. D2, a deiodinase abundant in the brain, has also been found to be abundant in skeletal muscle in humans, and levels may be increased in critical illness. The significance of these findings is uncertain at present.

2. Alterations in the pituitary–thyroid axis.

a. Synthesis and secretion of thyroid hormone are under the control of the anterior pituitary hormone, thyrotropin (TSH), in a classic negative feedback system.

b. While serum TSH levels are usually normal early in acute illness, levels often fall as the illness progresses due to the effects of a variety of inhibitory factors that are common in the treatment of the critically ill patient (Table 84-7).

c. The use of dopamine, increased levels of glucocorticoids, either endogenous or exogenous, and inhibitory signals from higher cortical centers also may play a role in decreasing TSH secretion, as well as certain thyroid hormone metabolites that are increased in nonthyroidal illness.

3. Alterations in serum-binding proteins.

a. Both T4 (99.97% bound) and T3 (99.7% bound) circulate in the serum bound primarily to thyroxine-binding protein (TBG), and the binding of thyroid hormones to TBG is affected by a variety of factors in acute illness (Table 84-8).

b. Since only the unbound hormone has any metabolic activity (free hormone concept), changes in the concentrations of, or binding to,

TABLE 84-7 Factors that Alter TSH Secretion

Increase	Decrease
Chlorpromazine	Acute and chronic illness
Cimetidine	Adrenergic agonists
Domperidine	Caloric restriction
Dopamine antagonists	Carbamazapine
Haloperidol	Clofibrate
Iodide	Cyproheptadine
Lithium	Dopamine and dopamine agonists
Metoclopramide	Endogenous depression
Sulfapyridine	Glucocorticoids
X-ray–contrast agents	IGF-1
	Metergoline
	Methylsergide
	Opiates
	Phenytoin
	Phentolamine
	Pimozide
	Somatostatin
	Serotonin
	Surgical stress
	Thyroid hormone metabolites

IGF-1, insulin-like growth factor–1.

TBG would have major effects on the total serum hormone levels but minimal changes in the free hormone concentrations, and, thus, overall thyroid function, are actually seen.

4. **Stages of the sick euthyroid syndrome.**
   a. **Low T3 state.**
      i. Common to all of the abnormalities in thyroid hormone concentrations seen in critically ill patients is a substantial depression of serum T3 levels, which can occur as early as 24 hours after the onset of illness and affects over half of the patients admitted to the medical service.
      ii. The decrease in serum T3 levels can be explained solely by inhibition of D1 and subsequent impairment of peripheral T4-to-T3 conversion.
      iii. Clinically, these patients appear euthyroid, although mild prolongation in Achilles reflex time is found in some patients.
      iv. This stage is common in patients with CHF and with acute cardiac injury. In patients with cardiac disease, serum T3 concentrations are a negative prognostic factor and inversely proportional to mortality.

TABLE 84-8 Factors that Alter Binding of Thyroxine (T4) to Thyroxine-Binding Protein

	Increase binding	Decrease binding
Drugs		
	Estrogens	Glucocorticoids
	Methadone	Androgens
	Clofibrate	L-asparaginase
	5-Fluorouracil	Salicylates
	Heroin	Mefenamic acid
	Tamoxifen	Antiseizure medications (phenytoin, tegretol)
	Raloxifene	Furosemide
		Heparin
		Anabolic steroids
Systemic factors		
	Liver disease	Inherited
	Porphyria	Acute illness
	HIV infection	Nonesterified free fatty acids
	Inherited	

HIV, human immunodeficiency virus.

b. High T4 state.

i. Serum T4 levels may be elevated early in acute illness due to either the acute inhibition of T4-to-T3 conversion or increased TBG levels.

ii. Increased serum T4 levels are seen most often in the elderly and in patients with psychiatric disorders.

iii. As the duration of illness increases, nondeiodinative pathways of T4 degradation increase and return serum T4 levels to the normal range.

c. Low T4 state.

i. As the severity and the duration of the illness increase, serum total T4 levels may decrease into the subnormal range as a result of a decrease in the binding of T4 to TBG, a decrease in serum TSH levels leading to decreased production of T4, and an increase in nondeiodinative pathways of T4 metabolism.

ii. The decline in serum T4 levels correlates with prognosis in noncardiac ICU patients, with mortality increasing as serum T4 levels drop below 4 μg/dL and approaching 80% in patients with serum T4 levels <2 μg/dL.

iii. Despite marked decreases in serum total T4 and T3 levels to the hypothyroid range, the free hormone levels are often normal; therefore, the low T4 state is more likely a marker of multisystem failure in these critically ill patients than a true hormone-deficient state.

d. Recovery state.

i. The alterations in thyroid hormone concentrations resolve as the illness resolves.

ii. This stage may be prolonged and is characterized by the modest increases in serum TSH levels.

iii. Full recovery, with restoration of thyroid hormone levels to the normal range, may take up to several months after the patient is discharged from the hospital.

D. Diagnosis.

1. The routine screening of an ICU population for the presence of thyroid dysfunction is not recommended due to the high prevalence of abnormal thyroid function tests and low prevalence of true thyroid dysfunction.

2. Whenever possible, it is best to defer routine evaluation of the thyroid–pituitary axis until the patient has recovered from his/her acute illness.

3. When thyroid function tests are ordered in a hospitalized patient, it should be with a high clinical index of suspicion for the presence of thyroid dysfunction.

4. Because every test of thyroid hormone function can be altered in the critically ill patient, no single test can definitively rule in or rule out the presence of intrinsic thyroid dysfunction (Table 84-9).

5. Thyroid function tests.

a. TSH assays.

i. While the sensitive TSH assay is currently the best screening test for thyroid dysfunction in the healthy, ambulatory patient, this does not hold true for the ill patient.

ii. Abnormal TSH values have been reported in up to 20% of hospitalized patients, over 80% of whom have no intrinsic thyroid dysfunction on follow-up testing when healthy.

iii. Abnormal TSH values require additional biochemical and clinical evaluation before a diagnosis of thyroid dysfunction can be made.

b. Free T4 concentrations.

i. Total T4 measurements alone are of little use in the acutely ill patient, since abnormalities in binding to serum proteins are commonplace.

ii. Measurement of true serum free T4 concentrations is time consuming and expensive; therefore, estimates of the free T4 concentrations are obtained by either the free T4 index (FTI) or the free T4 by analog measurement.

c. Total T3.

i. There is no indication for the routine measurement of serum T3 levels in the initial evaluation of thyroid function in the critically ill patient, since serum T3 concentrations are affected to the greatest degree by the alterations in thyroid hormone economy resulting from acute illness.

ii. The only setting where serum T3 levels may be helpful is in the presence of a suppressed sensitive TSH value where an elevated serum T3 concentration may differentiate between thyrotoxicosis and the sick euthyroid syndrome.

TABLE 84-9 Tests of Thyroid Function in the ICU

Tests	Typical normal range	Use	Limitation in acute illness
TSH	0.4–5.0 mU/L	Best initial test to determine thyroid status in healthy patients	Loss of specificity, abnormal in up to 20% of hospitalized patients
Total T4	4–12 µg/dL	Measures bound and free hormone in serum	Affected by alterations in serum-binding proteins
T4- or T3-resin uptake	25%–35%	Estimate of the serum protein-binding sites	Affected by alterations in serum-binding proteins
THBR	0.8–1.15	Estimate of the serum protein-binding sites	Affected by alterations in serum-binding proteins
FTI	1–4 (if use resin uptake) 4–12 (if use THBR)	Estimate of free T4 concentrations	Affected by alterations in serum-binding proteins
Free T4, analog method	0.7–2.1 ng/dL	Direct measurement of free T4 concentrations	May not be any more reliable than FTI
Free T4, equilibrium dialysis method	0.7–2.1 ng/dL	Gold standard for measurement of free T4 concentrations	Expensive, time consuming to perform, not readily available
Total T3	75–180 ng/dL	Measures bound and free hormone in serum	Levels fall in all hospitalized patients, never a first-line test
Free T3	200–400 pg/dL	Direct measurement of free T3 concentrations	No advantage to total T3
Thyroid autoantibodies (anti-Tg, anti-TPO)	Negative	Determines presence of autoimmune thyroid disease	Second-line test, may help predict presence of thyroid dysfunction

TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine; THBR, thyroid hormone–binding ratio; FTI, free T4 index; Tg, thyroglobulin; TPO, thyroid peroxidase.

d. Thyroid autoantibodies.
  i. The presence of thyroid autoantibodies (antithyroglobulin and antithyroid peroxidase) determines the presence of autoimmune thyroid disease but does not necessarily indicate thyroid dysfunction.
  ii. Thyroid autoantibodies do add to the specificity of abnormal TSH and FTI values in diagnosing intrinsic thyroid disease.

6. Diagnostic approach.
a. A reasonable initial approach is to obtain both FTI (or FT4) and TSH measurements in patients with a high clinical suspicion for intrinsic thyroid dysfunction.
b. Assessment of these values in the context of the duration, the severity, and the stage of illness of the patient will allow the correct diagnosis in most patients.
c. If the diagnosis is still unclear, measurement of thyroid antibodies may be helpful as a marker of intrinsic thyroid disease.
d. Only in the case of a suppressed TSH and a mid-normal to high FTI, the measurement of serum T3 levels is indicated.

E. Treatment.

1. Starvation/undernutrition.
a. L-T3 treatment results in increased protein breakdown and increased nitrogen excretion in fasting normal and obese patients.

2. General ICU patients.
a. No benefit of L-T4 on general medical patients, burn patients, patients with acute renal failure, or renal transplant.

3. Premature infants.
a. No benefit of L-T4 on developmental indices of premature infants at 26 to 28 weeks gestation.
b. Possible beneficial effect of L-T4 on infants of at 25 to 26 weeks gestation but possible deleterious effects on infants of 27 to 30 weeks gestation.
c. No benefit of L-T3.
d. Meta-analysis shows no significant effects of thyroid hormone treatment of premature infants.

4. Cardiac surgery patients.
a. Small studies suggest improved hemodynamic parameters with L-T3.
b. Large trials show no benefit of L-T3 noted in patients undergoing cardiac bypass.
c. Possible improvement in hemodynamic parameters and hospital stay with L-T3 in children undergoing cardiac bypass surgery.

5. Cardiac donors.
a. Variable results on the effects of L-T3 in preserving function of normal hearts in brain-dead cardiac donors before transplantation.
b. Possible benefits of L-T3 in improving function of impaired hearts before transplant, potentially increasing the pool of organs available for transplantation.
c. Consensus conferences recommend the use of L-T3 as part of the hormonal resuscitation in donors whose cardiac ejection fraction is <45%.

6. Congestive heart failure.
   a. A small uncontrolled study suggested that short-term L-T4 therapy increased cardiac output and functional capacity and decreased systemic vascular resistance.
   b. Improved hemodynamic parameters and neurohumerol profiles with short-term intravenous L-T3 infusion, possibly requiring supraphysiologic concentrations.

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85 Hypoadrenal Crisis and the Stress Management of the Patient on Chronic Steroid Therapy

Neil Aronin

I. HYPOADRENAL CRISIS

A. General principles.

1. The adrenal glands secrete five types of hormones, but two are critical in the intensive care unit (ICU) setting.
   a. Aldosterone has a major effect on electrolyte balance.
   b. Cortisol promotes gluconeogenesis and has many other actions.
   c. Both are life sustaining; deficiency of either can result in a hypoadrenal crisis.
2. Hypoadrenal crisis can occur as an acute event in individuals lacking previous adrenal problems.
3. A high index of suspicion arises in patients who have inadequate responses to initial therapies.
4. Severe illnesses that contribute to ICU admission (e.g., sepsis, acute respiratory failure) might interfere with traditional tests of adrenal function.
5. There is no unified alogorithm of treatment.

B. Etiology.

1. The most common cause of primary adrenal failure, Addison disease, is autoimmune and is often known before the ICU admission.
2. Other causes of adrenal failure offer a difficult diagnosis in the ICU. These include overwhelming sepsis; hemorrhage secondary to trauma, circulating anticoagulants, or anticoagulant therapy; tuberculosis; fungal disease; amyloidosis; acquired immune deficiency syndrome; antiphospholipid syndrome; infarction; irradiation; metastatic disease; or drugs.
3. Critical illness can cause or bring out adrenal insufficiency.
4. The most common cause of secondary adrenal insufficiency is suppression of corticotrophin (adenocorticotrophic hormone [ACTH]) release by prior glucocorticoid therapy.
   a. There are no cutoffs on duration of glucocorticoid therapy, its route of administration, and its dosage that can cause adrenal cortical atrophy and inadequate reserve.

C. Pathophysiology.

1. The adrenal cortex secretes aldosterone from the zona glomerulosa and cortisol from the zona fasciculata.
2. Aldosterone promotes the reabsorption of sodium and the secretion of potassium and hydrogen ion in the distal renal tubule.

a. It is controlled mainly by the renin–angiotensin system.
b. Glucocorticoid suppression of ACTH, and therefore cortisol in the zona fasciculata, does not suppress aldosterone in the zona glomerulosa.
c. Aldosterone deficiency results in sodium wasting, with concomitant loss of water and an increase in renal reabsorption of potassium. A decrease in plasma volume and dehydration occurs, with subsequent increases in blood urea nitrogen (BUN) and plasma renin activity.

3. Glucocorticoids promote gluconeogenesis and protein wasting and increase the excretion of free water by the kidney.
   a. In large doses, glucocorticoids bind to mineralocorticoid receptors, increasing sodium reabsorption and potassium and hydrogen ion excretion.
   b. Glucocorticoids act on the central nervous system, to affect the sense of well-being, appetite, and mood. They inhibit ACTH release through hypothalamic and pituitary actions.
   c. Glucocorticoids have direct effects on the cardiovascular system and maintain blood pressure, although mechanisms are not established. Critical illness and glucocorticoid deficiency affect common physiologic systems.
   d. Excess glucocorticoids cause lymphopenia, leukocytosis, and eosinopenia; can lead to osteoporosis and reduction of hypercalcemia; and can impair host defenses to infections.
   e. A decrease in circulating levels of cortisol causes a marked increase in levels of ACTH and β-lipotropin, from which melanocyte-stimulating hormone activity increases. In long-standing adrenal insufficiency, the skin, especially creases and scars, develops hyperpigmentation.
   f. Low plasma cortisol is also associated with the following:
      i. Orthostatic hypotension, which can progress to frank shock in a crisis.
      ii. Hypoglycemia and an increase in sensitivity to insulin.

D. Diagnosis.

1. Clinical manifestations that suggest adrenal insufficiency include the following:
   a. A history of increasing weakness, lassitude, fatigue, anorexia, vomiting, and constipation (with hypoadrenal crisis, diarrhea can occur).
   b. Patients who present with adrenal hypofunction in crisis are hypotensive (volume depletion) or in frank shock; they generally have a fever, sometimes high, and may be stuporous or comatose.
   c. In individuals whose loss of adrenal function occurs precipitously (adrenal hemorrhage due to an infection, anticoagulant therapy, trauma, or after surgery), no hyperpigmentation is seen but flank pain is often present.
   d. Severely ill patients are often suspected of developing adrenal hypofunction, but actual incidence is not established.
   e. Critical illness may be associated with glucocorticoid resistance that further complicates recognition of adrenal dysfunction.
   f. In secondary adrenal failure caused by a lack of ACTH, the signs and symptoms are essentially those of glucocorticoid deficiency, especially hypoglycemia. ACTH deficiency generally follows deficiency in other

anterior pituitary hormones, so that deficits in overall pituitary secretion can lead to signs of dysfunction of other endocrine glands.

2. Adrenal function tests.
   a. In critical illness, the diagnosis of hypoadrenal function is less apparent than it is in the ambulatory setting.
   b. In primary adrenal insufficiency, plasma concentrations of cortisol are usually low or in the low-normal range and do not rise after ACTH stimulation.
   c. The failure to respond to ACTH is the definitive test for primary adrenal hypofunction.
      i. Administering 250 μg of cosyntropin (Cortrosyn) (synthetic ACTH 1-24) intravenously (IV) leads to a 9 μg increase of cortisol over baseline at 30 or 60 minutes, or a stimulated cortisol level ≥20 μg/dL, constitutes an adequate adrenal response.
   d. Severe illness can interfere with the adrenal response to ACTH. Recognition of the complexity of adrenal hypofunction in critical illness has led to reconsideration of its diagnosis in the ICU.
      i. A serum-free cortisol of <9 μg/dL is sufficient to initiate glucocorticoid replacement.
      ii. However, measurement of free cortisol is currently unavailable in most hospitals, so that a random, total cortisol of <10 μg/dL is used as a threshold for glucocorticoid therapy.
      iii. The American College of Critical Care considers this recommendation to be weak with moderate quality of evidence. The concept of situational adrenal insufficiency is an idea inchoate, but a threshold concentration of total cortisol provides a guideline for intervention.
      iv. The term critical illness–related corticosteroid insufficiency is preferred in considering adrenal function in severe illness, because of the uncertainties in diagnosis.
3. In acute adrenal insufficiency, as a result of adrenal hemorrhage, a computed tomography (CT) scan of the adrenal glands can be a useful diagnostic tool.
4. Individuals with adrenal hypofunction generally show varying degrees of hyponatremia and hyperkalemia, and the sodium:potassium ratio is almost always <30.

E. Treatment.

1. The management of the hypoadrenalism has been vetted by a committee of international experts and the American College of Critical Care Medicine.
2. Recommendations have been provided as guidelines for usefulness of glucocorticoid therapy in hypoadrenal function and critical illness. There is agreement that hypoadrenalism needs to be treated.
   a. In critical illness in which primary adrenal function is suspected (e.g., evidence for hemorrhage), a bolus of 100 mg of hydrocortisone should be administered IV and then 100 mg IV over the next 24 hours.
   b. After the initial therapy and stabilization of the patient, hydrocortisone can be decreased by 50% each day.
   c. Maintenance dose is 20 to 30 mg/day. Fludrocortisone 0.1 mg/day is started once the maintenance glucocorticoid dose is started.

3. It is not established whether adrenal insufficiency is a prerequisite for use of glucocorticoids in septic shock or early severe adult respiratory distress syndrome.
   a. Few studies look sufficiently at large subject groups for proper anaylsis.
   b. The corticosteriod therapy of septic shock (CORTICUS) study showed no effect of glucocorticoid treatment of outcome in shock.
      i. The placebo group yielded a 32% mortality, and the glucocorticoid treated group had a 35% mortality.
   c. There is a weak recommendation based on moderate-quality evidence for use of glucorticoids early in severe shock, as compelling data for this recommendation are unavailable.

II. GLUCOCORTICOID USE IN STRESSED PATIENTS ON GLUCOCORTICOID TREATMENT

A. General principles.

1. In healthy subjects, the secretion rate of cortisol increases from 10 mg/day to 50 to 150 mg/day during surgical procedures but rarely exceeds 200 mg/day. The degree of adrenal response depends, in part, on the extent and duration of surgery.
2. The development of shock in the acutely ill or surgical patients on steroid therapy (or after withdrawal within 1 year) should not be attributed solely to diminished adrenal responsiveness.
3. Adrenal steroids can and should be administered, but other contributing causes of hypotension should be sought.
4. Suppression of the hypothalamic–anterior pituitary–adrenal axis can occur as early as 5 days after initiation of glucocorticoid treatment.
   a. After long-term administration of corticosteroids, the adrenal axis may respond poorly to appropriate stimuli up to 1 year after steroid withdrawal.
   b. Adrenal suppression cannot be predicted based on glucocorticoid dosage and duration of a normal basal cortisol.

B. Diagnosis.

1. Patients on glucocorticoid therapy for at least 4 weeks at either pharmacologic or replacement levels and those who have stopped glucocorticoids within the last year have the highest risk for adrenal suppression.
2. Time permitting, a Cortrosyn test provides information on the adequacy of the adrenal response to stress.
   a. An adequate increase in cortisol following corticotrophin administration is interpreted to indicate the presence of an intact hypothalamic–anterior pituitary–adrenal axis.
   b. Patients who have a subnormal response to Cortrosyn also have a subnormal cortisol response to stress or surgery.

C. Treatment.

1. For minor surgical procedures, the patient's usual dose of glucocorticoid is probably sufficient, but a single dose of 25 mg hydrocortisone or its equivalent can be given instead.

2. As the extent and duration of surgery increase, the glucocorticoid dose should be increased from 50 to 75 mg/day hydrocortisone or its equivalent for up to 2 days, to 100 mg to 150 mg hydrocortisone or its equivalent for up to 3 days.
3. Hydrocortisone can be rapidly tapered and the patients returned to their usual dose of glucocorticoid if needed.

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86 Disorders of Mineral Metabolism

Seth M. Arum and Daniel T. Baran

I. GENERAL PRINCIPLES

A. Disorders of mineral metabolism (calcium, magnesium, phosphorus) occur frequently in patients admitted to ICUs. They are rarely the primary cause for admission, but they may exacerbate existing medical situations.

B. Calcium, magnesium, and phosphorus metabolisms are controlled by interaction of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25 D), and calcitonin.

II. CALCIUM DISORDERS

A. Pathophysiology.

1. In extracellular fluids, calcium is free (40%) and bound to albumin or other anions (60%). The free (ionized) form is biologically active. Measurements of total serum calcium should be corrected for the albumin level with the following equation: Corrected calcium = Measured calcium + (0.8 × [4 – Measured albumin].).

2. Changes in acid–base balance affect binding of calcium to albumin.

a. Acidosis decreases binding and increases the free form.

b. Alkalosis increases binding and decreases the free form.

3. Calcium balance depends on bone resorption and formation, intestinal absorption, and renal excretion.

a. Persistent PTH exposure increases bone resorption and renal calcium reabsorption.

b. 1,25 D enhances intestinal calcium absorption.

c. Calcitonin inhibits bone resorption and increases renal calcium excretion.

B. Diagnosis of hypercalcemia.

1. Signs and symptoms.

a. Mental manifestations vary from stupor to coma.

b. Neurologic effects include reduced muscle tone and reflexes.

c. Intestinal and urologic signs include vomiting, polyuria, polydipsia, and constipation.

d. Cardiovascular effects include shortening of the QT interval and increasing the potential for arrhythmias.

2. Differential diagnoses can be divided into PTH independent and PTH dependent.

a. PTH independent (PTH level will be suppressed) is more common in ICU patients.
   i. Malignancy—especially lung, head and neck, breast, hematologic (myeloma and lymphoma), and renal cell carcinoma.
   ii. Granulomatous disease.
   iii. Immobilization.
   iv. Milk-alkali syndrome.
   v. Thyrotoxicosis.
   vi. Vitamin D or A intoxication.
   vii. Addison's disease.
   viii. If PTH is suppressed (PTH independent), then thyroid-stimulating hormone, PTH-rP, 1,25 D levels, and urine/serum protein electrophoreses can help establish the diagnosis.
b. PTH dependent (PTH level will be high or normal) is more common in outpatients.
   i. Hyperparathyroidism from adenoma, hyperplasia, or carcinoma (rare).
   ii. Familial hypocalciuric hypercalcemia (FHH).

C. Treatment of hypercalcemia.

1. Isotonic saline hydration.
   a. Pivotal because response is rapid. Aim is to achieve a urine output of 3 to 5 L/24 hours, usually requiring 200 to 500 mL/hour of normal saline.
   b. Furosemide (Lasix) 20 to 40 mg intravenously (IV) once rehydration has been achieved—prevents fluid overload and inhibits renal calcium reabsorption. Electrolyte measurement is mandatory.
2. Calcitonin.
   a. Inhibits bone resorption when a rapid decrease is required.
   b. Dose is 4 to 8 international units/kg body weight subcutaneously or intramuscularly every 12 hours with hydration.
   c. Decrease in serum calcium 2 hours after dose and lasts 6 to 8 hours. Average decrease is 9% and lasts 4 to 7 days (tachyphylaxis occurs).
3. Bisphosphonates.
   a. Inhibit bone resorption and provide a more prolonged calcium decrease.
   b. Pamidronate (Aredia) 60 to 90 mg IV over 2 hours, with hydration.
   c. Zoledronate (Zometa) 4 mg IV over not < 15 minutes, with hydration.
      i. Calcium normalizes in 60% to 90% of patients with significant decreases within 4 days and duration of response between 1 and 3 weeks.
      ii. Renal function needs to be monitored.
      iii. Retreatment after a minimum of 7 days to allow full response to initial dose. Dose and manner of retreatment identical to initial treatment.

D. Diagnosis of hypocalcemia.

1. Signs and symptoms.
   a. Neurologic manifestations include hyperreflexia and tetany.
   b. Chvostek sign—facial muscle spasm by tapping the facial nerve.
   c. Trousseau sign—carpal spasm elicited with a blood pressure cuff inflated above systolic pressure for 3 minutes.

2. Differential diagnosis.
   a. Hypoparathyroidism.
   b. Vitamin D deficiency.
   c. Hyperphosphatemia.
   d. Magnesium deficiency.
3. PTH, 25-hydroxyvitamin D, magnesium, and phosphorus levels (measured prior to IV calcium) usually identify the cause.

E. Treatment of hypocalcemia.

1. Depends on severity and chronicity. Symptomatic patients should receive IV calcium.
2. Calcium gluconate 10% can be administered as follows:
   a. 10 mL administered in 100 mL of 5% dextrose in water over 10 minutes.
   b. Often followed by a continuous intravenous infusion containing 10 ampules (10-mL vials) in 1 L of 5% dextrose in water running at 50 mL/hour. Total calcium should be maintained between 8 and 8.5 mg/dL and not higher to avoid hypercalciuria.
3. Concurrent oral calcium should be given to provide 500 to 1,000 mg of elemental calcium three times daily.
4. Vitamin D.
   a. Cholecalciferol 800 to 1,500 international units by mouth (PO) daily or ergocalciferol 50,000 international units PO weekly. Slow onset but wide safety margin.
   b. 1,25 D (Rocaltrol) 0.25 to 2.0 μg PO daily. More rapid and potent than ergocalciferol, but narrower safety margin—can cause hypercalciuria or hypercalcemia.

III. MAGNESIUM DISORDERS

A. Pathophysiology.

1. Magnesium circulates in the free form (70%) and bound to albumin (30%). Albumin needs to be measured to interpret magnesium levels.
2. Magnesium levels depend on intestinal absorption and renal excretion.
   a. Decreased renal excretion (e.g., renal failure) increases magnesium levels.
   b. Increased renal excretion (e.g., osmotic diuresis or drugs [ethanol, aminoglycosides, cisplatin]) decreases renal resorption of filtered magnesium.
   c. Decreased intestinal absorption (e.g., accompanying fat malabsorption) decreases magnesium levels.

B. Diagnosis of hypermagnesemia.

1. Signs and symptoms.
   a. Central nervous system depression (e.g., decreased reflexes, flaccid paralysis, stupor, coma).
2. Etiology.
   a. Most common cause is renal failure, aggravated by use of magnesium-containing antacids.

b. The hypermagnesemia associated with diabetic ketoacidosis usually reflects dehydration and masks total body magnesium depletion.

c. As a complication of intravenous magnesium therapy in the setting of obstetrical uses including the treatment of preeclampsia.

C. Treatment of hypermagnesemia.

1. Dialysis for the symptomatic patient when renal function is impaired.

2. If renal function is not impaired, magnesium excretion can be increased by furosemide 20 to 40 mg IV every 1 to 2 hours. Electrolytes must be monitored.

3. Neuromuscular depressant effects of magnesium in the symptomatic patient can be acutely antagonized by calcium gluconate 1 to 2 g administered in 100 mL 5% dextrose in water over 5 to 10 minutes. Serum calcium levels must be monitored.

D. Diagnosis of hypomagnesemia.

1. Signs and symptoms.

a. Central nervous system excitability which in part may be caused by hypocalcemia. Low magnesium impairs PTH secretion and peripheral responsiveness to PTH, which may result in hypocalcemia.

2. Etiology.

a. Increased renal excretion due to osmotic diuresis or medications (see Section III.A.2.b) is the most common cause.

b. Frequently present in patients with malabsorption.

c. Often encountered in the alcoholic patient due to poor dietary intake and increased renal excretion.

E. Treatment of hypomagnesemia.

1. A symptomatic patient usually has a total body magnesium deficit of 1 to 3 mEq/kg body weight.

2. Magnesium oxide (Mag-Ox 400) 1 to 2 tablets PO daily (241 mg [19.86 mEq] of magnesium per tablet.).

3. In the symptomatic patient who cannot take oral medications, magnesium sulfate (100 mg [8 mEq] magnesium per vial) IV can be used. Administer 3 to 4 g magnesium sulfate over 12 to 24 hours. Can be repeated as necessary to keep levels >1.2 mg/dL. Reduce by 75% if renal failure is present.

IV. PHOSPHORUS DISORDERS

A. Pathophysiology.

1. Most nonskeletal phosphorus is found intracellularly. Because of shifts between the intra- and extracellular compartments, serum phosphorus does not reflect body stores.

a. Acidosis causes shift of phosphorus from within cells to the extracellular compartment. Serum phosphorus levels may be normal in the acidotic patient despite depletion of total body stores due to this shift. As the acidosis is corrected, serum phosphorus levels may fall.

b. Low serum phosphorus stimulates renal production of 1,25 D.

c. Fibroblast growth factor-23 (FGF-23) has been found to play an essential role in phosphorus and vitamin D metabolism, but the clinical significance is unclear, and it is not routinely measured in practice.

B. Diagnosis of hyperphosphatemia.

1. Signs and symptoms—No clinical signs or symptoms of hyperphosphatemia per se. Hyperreflexia and tetany may occur due to accompanying hypocalcemia.

2. Differential diagnosis—Most often encountered in patients with renal failure or hypoparathyroidism. In both clinical situations, hyperphosphatemia results from impaired renal excretion. Can also be seen from cellular lysis such as rhabdomyolysis and tumor lysis syndrome.

C. Treatment of hyperphosphatemia.

1. Restriction of dietary phosphorus intake.

2. Correction of accompanying hypocalcemia (see Section II.E.2).

3. Phosphate binders.

a. Calcium acetate 667 mg, 2 tablets PO with meals.

b. Sevelamer 800 mg, 1 to 2 tablets PO with meals is preferred in patients with elevated calcium × phosphate products.

D. Diagnosis of hypophosphatemia.

1. Signs and symptoms—muscle weakness, rhabdomyolysis.

2. Differential diagnosis.

a. Impaired intestinal absorption (e.g., malnutrition or use of phosphate-binding antacids).

b. Increased renal excretion (e.g., hyperparathyroidism, vitamin D deficiency [due to secondary hyperparathyroidism], hyperglycemic states [due to osmotic diuresis], impaired renal handling of phosphorus [vitamin D–resistant rickets]).

E. Treatment of hypophosphatemia.

1. Severe hypophosphatemia (<1.0 mg/dL) requires parenteral therapy.

a. Sodium phosphate 40 mmol in 5% dextrose in water IV over 2 hours.

b. Hypercalcemic patients or patients with renal failure should receive 50% less to avoid hyperphosphatemia and metastatic calcification.

2. Mild hypophosphatemia—Potassium phosphate (K-Phos Neutral) 2.5 to 3.5 g phosphorus/day PO in divided doses.

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87 Hypoglycemia

John P. Mordes and Samir Malkani

I. GENERAL PRINCIPLES

A. Hypoglycemia is common and must be excluded in every patient with stupor or coma.

B. Cases of refractory, prolonged hypoglycemia of unknown etiology require ICU admission.

C. Severe hypoglycemia can lead to permanent neurologic damage.

D. No specific blood glucose concentration uniformly defines hypoglycemia.

1. Typically <50 mg/dL (2.8 mM).
2. Physiologic definition: blood glucose low enough to cause release of counterregulatory hormones and impair mental status.

E. "Whipple triad" defines hypoglycemia best.

1. Documentation of a low glucose concentration.
2. Concurrent symptoms of hypoglycemia.
3. Resolution of symptoms after administration of glucose.

II. PATHOPHYSIOLOGY

A. Hypoglycemia can be divided into fasting and nonfasting categories.

1. "Nonfasting," "postprandial," "reactive" hypoglycemic states are, with one exception, not usually life threatening and can be managed on an outpatient basis.
2. Exception: postprandial hypoglycemia after gastric bypass surgery.

B. Hypoglycemia has several etiologies.

1. Excess insulin.
   - **a.** Insulin overdose.
     - **i.** The commonest cause of hypoglycemia.
     - **ii.** In most cases, the overdose is inadvertent, due to a missed meal or intense exercise.
     - **iii.** Suspect intentional medication overdose in anyone with access to insulin or oral hypoglycemic agents who has unexplained hypoglycemia.
     - **iv.** Long-standing diabetes causes increased sensitivity to short-acting insulins, defective counterregulatory responses, and more severe hypoglycemia.
     - **v.** When counterregulation is impaired, adrenergic symptoms (e.g., tremor, diaphoresis, tachycardia) may not occur and neuroglycopenic symptoms (e.g., confusion, combativeness, seizure, coma) can develop rapidly.

vi. Inadequate counterregulation also delays recovery from hypoglycemia.

2. Intensive insulin therapy.
   a. Efforts to achieve near-normal glucose in the ICU and in some ambulatory patients are associated with high rates of hypoglycemia and *no* improvement in outcome.
3. Hypoglycemia due to oral medications.
   a. "Hypoglycemic agents" augment insulin secretion.
      i. The sulfonylurea-class oral hypoglycemic agents are the leading cause of hypoglycemia in persons over 60, usually in the setting of starvation superimposed on liver or kidney impairment.
      ii. Overdoses of sulfonylureas also cause hypoglycemia in younger persons. Oral hypoglycemic agent pharmacy errors (e.g., chlorpropamide for chlorpromazine) have been reported.
      iii. The meglitinides also cause hypoglycemia. Surreptitious abuse of repaglinide has been reported.
      iv. The incretins and DPP-4 inhibitors enhance insulin secretion, but only in response to oral glucose ingestion, so they rarely cause hypoglycemia when used as monotherapy. Combined with insulin or oral agents they increase the risk of hypoglycemia.
   b. "Antidiabetic agents" promote normoglycemia via other mechanisms. These include metformin, thiazolidinediones, and alpha-glucosidase inhibitors.
      i. When given as monotherapy they seldom cause hypoglycemia.
      ii. They increase the likelihood of hypoglycemia when used in combination with insulin or oral hypoglycemic drugs.
      iii. Metformin is sold in fixed-ratio tablets in combination with other drugs such as sulfonylureas and thiazolidinediones; overdosage with a combination drug can cause severe hypoglycemia.
      iv. Because alpha-glucosidase inhibitors interfere with the digestion of carbohydrates, hypoglycemic patients treated taking these drugs plus insulin or sulfonylureas may not respond to therapy with oral complex sugars.
4. Several medications not used to treat diabetes can increase circulating insulin concentration and cause hypoglycemia. Some are listed in Table 87-1.
5. Insulinomas and other causes of hyperinsulinemia.
   a. Insulin-secreting pancreatic islet cell tumors are rare and usually cause fasting hypoglycemia.
   b. Paraneoplastic hypoglycemia may be caused by tumors that secrete insulin-like growth factors.
   c. An unusual cause of hypoglycemia in children is nesidioblastosis (nonmalignant islet cell adenomatosis).
   d. Gastric bypass surgery leads to postprandial hypoglycemia in some patients years after surgery. Some cases are due to dumping syndrome and are self-limiting; others are associated with hyperinsulinemia, possibly as a result of nesidioblastosis, though this is disputed.
   e. Autoimmune or antibody-mediated hypoglycemia is a rare condition in which autoantibodies activate the insulin receptor.

TABLE 87-1 Drugs and Toxins Associated with Hypoglycemia

Agents that increase circulating insulin

Stimulants and enhancers of insulin secretion
- ***Sulfonylureas*** (glyburide, glipizide, glibenclamide)
- ***Meglitinides*** (repaglinide [Prandin], nateglinide [Starlix])
- Incretin memetics (exenatide [Byetta], liraglutide [Victoza])
- DPP-4 inhibitors (Sitagliptin-Januvia, Saxagliptin-Onglyza)
- β-2 adrenergic agonists (e.g., Albuterol Calcium)
- ***Chloroquine (Aralen)***
- ***Cibenzoline***
- Disopyramide (Norpace)
- Quinidine
- ***Quinine***
- Ritodrine (Yutopar)
- Terbutaline
- Trimethoprim/sulfamethoxazole (Bactrim)

Agents that impair gluconeogenesis

Hepatotoxins
- Acetaminophen (Tylenol, Tempra)
- ***Propoxyphene (Darvon)***
- Amanitatoxin

Uncertain or other mechanisms of action

- ACE inhibitors Acetazolamide (Diamox)
- Aspirin
- Aluminum hydroxide (Dialume)
- Anabolic steroids
- Azapropazone
- Chlorpromazine (Thorazine)
- Cimetidine
- ***Ciprofloxacin, gatifloxacin, clinafloxacin***
- Clofibrate
- Dandelions
- Dexmedetomidine
- Diphenhydramide
- Doxepin (Sinequan, Adapin)
- "Ecstasy" (MDMA)
- Enflurane Formestane
- Ethylenediaminetetraacetic acid (Versene)
- Etanercept
- Etomidate
- Fenoterol
- Fluoxetine
- Haloperidol
- Halothane

Destruction of beta-cells with insulin release
Pentamidine (Pentam)
Streptozotocin

Agents that enhance the action of oral agents

Clarithromycin
Imipramine (Tofranil)
NSAIDs
Phenylbutazone (Butazolidin)
Salicylates
Sulfonamides
Warfarin (Coumadin)

Inhibition of gluconeogenesis
Akee fruit
Ethanol
Metformin
Metoprolol (Lopressor)
Nadolol (Corgard)
Phenformin
Pindolol (Visken)
Propranolol (Inderal)

Herbal extracts
Imatinib (Gleevec)
Indomethacin
Interferon-α
Isoxsuprine
Lidocaine
Lithium
Mefloquin
Nefazodone
NSAIDs
Orphenadrine
Oxytetracycline
Para-aminobenzoic acid
Para-aminosalicylic acid
Perhexiline
Phenytoin (Dilantin)
Rantidine (Zantac)
Salicylates
Selegiline
Sulfadiazine
Sulfisoxazole (Gantrisin)
Valproate

A sampling of common trade names is shown in parenthesis; the enumeration of trade names is not exhaustive. Data for many listed agents are very limited or anecdotal or involved treatment with more than one drug. Drugs for which better documentation is available are indicated in ***bold italic.***

6. Hypoglycemia associated with deficiencies in counterregulatory hormones.
   a. Adrenal disease leading to glucocorticoid deficiency can cause hypoglycemia in children.
   b. Hypopituitarism causes deficiencies of growth hormone, cortisol, and/or thyroid hormone.
   c. Glucagon deficiency is the rarest cause of hypoglycemia.
7. Hypoglycemia due to inadequate production of endogenous glucose.
   a. Liver disease seldom causes hypoglycemia until severe. Hepatotoxins that impair gluconeogenesis include CCl_4, the *Amanita phalloides* mushroom toxin, and urethane. Hepatic congestion due to severe congestive heart failure rarely causes hypoglycemia.
   b. Kidney disease is commonly associated with hypoglycemia, especially in diabetic patients undergoing dialysis. "Spontaneous" fasting hypoglycemia may occur in some nondiabetic patients with end-stage renal disease.
8. Alcohol-induced hypoglycemia (alcoholic ketoacidosis; discussed in greater detail in Chapter 83).
   a. Occurs because ethanol inhibits gluconeogenesis.
   b. Can occur more than a day after drinking in the setting of poor food intake and depleted glycogen stores.
   c. Ketonuria and ketonemia are usually present.
   d. Children and chronic alcohol abusers are most susceptible.
   e. Persons with diabetes who become intoxicated may develop life-threatening hypoglycemia as a result of the metabolic synergy of ethanol and insulin.
9. Drugs and poisons that do not increase circulating insulin can cause hypoglycemia; some are listed in Table 87-1.
   a. Beta-blockers impair gluconeogenesis and may mask adrenergic symptoms.
   b. Salicylates cause hypoglycemia commonly in children but rarely in adults.
10. Sepsis has occasionally been implicated in hypoglycemia. Septic hypoglycemic patients are often acidotic, and the fatality rate is high.
11. Congenital enzymatic deficiencies typically produce hypoglycemia in infancy in the context of glycogen storage disease or impaired hepatic gluconeogenesis.
12. Fasting hypoglycemia due to the unavailability of gluconeogenic substrate.
   a. An example is nonketotic hypoglycemia of childhood in which the basal concentration of the gluconeogenic precursor alanine is low.

III. DIAGNOSIS

A. Clinical presentation.

1. Adrenergic signs and symptoms.
   a. Caused by counterregulatory catecholamines.
   b. Weakness, palpitations, anxiety, diaphoresis, tachycardia, peripheral vasoconstriction, and widening of the pulse pressure.
   c. May be absent in patients on sympatholytic drugs or with long-standing diabetes.

2. Neurologic signs and symptoms.
   a. Early: hunger, headache, confusion, slurred speech, and other nonspecific behavioral changes.
   b. Later: lethargy, obtundation, seizures, and coma.
3. Cardiac manifestations of hypoglycemia and sympathoadrenal response.
   a. Supraventricular and ventricular tachycardias, atrial fibrillation, and junctional dysrhythmias.
   b. ECG abnormalities include T-wave flattening, increased QT interval, ST segment depression, and repolarization abnormalities.
   c. Bradycardias have also been attributed to hypoglycemia, but only rarely.
4. Prolonged hypoglycemia can be seen with hypothermia, hypokalemia, hypophosphatemia, and respiratory failure.

B. Laboratory.

1. Obtain and save blood and urine samples from hypoglycemic patients when first seen. Assays for sulfonylureas or insulin may need to be performed later.
2. Blood glucose concentration.
   a. Is generally <50 mg/dL (<2.8 mM) when symptoms of hypoglycemia occur.
   b. Fingerstick blood glucose determinations are less accurate at the lower end of the scale and should be confirmed.
   c. After approximately 48 hours of starvation, many asymptomatic individuals have a plasma glucose <50 mg/dL (<2.8 mM). After 72 hours of fasting glucose, it may approach 40 mg/dL (2.2 mM).
   d. "Low" plasma glucose concentrations also occur in pregnancy during which the normal fasting glucose is 60 mg/dL or less (3.3 mM).
   e. "Factitious hypoglycemia": the result of storing blood samples at room temperature or large numbers of white blood cells (e.g., in leukemia).
3. Ketonuria.
   a. Low glucose is normally associated with low insulin levels that promote lipolysis and ketogenesis.
   b. Hypoglycemia with ketonuria is *unlikely* to be due to high insulin.
4. Detection of drugs and toxins.
   a. Oral agent abuse.
      i. Test serum and urine for sulfonylureas.
      ii. Must be specifically requested; not a part of routine toxin screens.
   b. Detection of surreptitiously injected insulin.
      i. When abusive insulin self-administration is suspected, obtain simultaneous insulin and C-peptide concentrations during hypoglycemia.
      ii. Insulin and C-peptide are cosecreted by beta-cells, but the latter is not present in commercial insulin.
5. Insulinomas are often small and difficult to visualize radiographically.
   a. In patients with suspected insulinoma, obtain fasting immunoreactive insulin (IRI, measured in microunits/mL) and glucose (mg/dL).

b. If the IRI/glucose ratio is >0.3, insulin may be inappropriately high.
c. Proinsulin is typically elevated to >30% of the insulin concentration in cases of insulinoma.

6. Other.
a. Always check hepatic and renal function.
b. Do a cosyntropin test if adrenal insufficiency is suspected.

IV. TREATMENT

A. Specific therapies.

1. Glucose.
a. Treat presumed hypoglycemia with an intravenous injection of 50 mL of D50W over 3 to 5 minutes.
i. This is lifesaving in hypoglycemic coma and harmless when given to patients with coma due to other causes.
ii. Avoid subcutaneous extravasation; D50W is hypertonic and can cause tissue damage and pain.
iii. Treatment with D50W usually improves mental status within minutes, but patients who are elderly or who have had prolonged hypoglycemia may respond slowly.
b. Most hypoglycemia can be treated with glucose alone. Recurrent severe hypoglycemia may require adjunctive therapy.
c. Alert, cooperative patients can be given oral carbohydrates (e.g., sucrose in orange juice or glucose tablets).
d. Oral treatment of hypoglycemia in patients taking alpha-glucosidase inhibitors should be with monomeric glucose or fructose (e.g., fruit juice).
e. The most common error in management is inadequate treatment leading to recurrence.
i. After the first bolus of D50W is given, an infusion of D5W or D10W glucose should be started in any patient whose hypoglycemic episode is not unequivocally due to exogenous short- or intermediate-acting insulin.
ii. Meals should be provided if the patient can eat.
iii. Severe cases of unexplained hypoglycemia require intensive care monitoring.
iv. Blood glucose should be monitored every 1 to 3 hours and the serum glucose concentration maintained at a target level of at least 100 mg/dL.
v. To determine whether parenteral glucose is no longer needed, the infusion should be discontinued and blood glucose concentration measured every 15 minutes.
vi. If a patient is unable to maintain a blood glucose concentration >50 mg/dL or if the patient becomes symptomatic, reinstitution of glucose therapy is necessary.
f. When the cause of hypoglycemia is sulfonylurea ingestion, patients should usually be admitted to the hospital because the half-life of many drugs in this class is >24 hours.

i. It is particularly important that glucose infusions be continued while such patients are asleep.
ii. Sulfonylurea overdose may require 2 to 3 days of intravenous glucose therapy.
iii. The somatostatin analog octreotide, which inhibits insulin secretion, may be helpful.

2. Glucagon.
   a. Glucagon is a useful drug principally in out-of-hospital treatment of hypoglycemia.
   b. Useful in the emergency department or ICU in a patient without intravenous access.
   c. Most effective in patients with ample liver glycogen stores.
3. Agents that block insulin secretion.
   a. If hypoglycemia is due to insulinoma or nesidioblastosis, it may (rarely) be necessary to add drugs that inhibit insulin secretion.
   b. Diazoxide and the somatostatin analog octreotide.
   c. In some cases, calcium channel blockers, alone or in combination with octreotide or alpha-glucosidase inhibitors, may be effective.
4. Consider efforts to prevent drug absorption and increase elimination.
   a. Activated charcoal adsorbs sulfonylureas.
   b. Urinary alkalinization may enhance sulfonylurea excretion.
   c. Charcoal hemoperfusion is probably not indicated except in renal failure and massive overdose.
5. Steroids.
   a. Glucocorticoids may be useful in severe, refractory hypoglycemia of obscure etiology.
   b. Increase gluconeogenic substrates and inhibit insulin action.

B. Key points and pitfalls.

1. Manage the precipitating factor(s).
2. Glucose corrects hypoglycemia but not its cause.
3. The commonest cause of hypoglycemia is inadvertent insulin overdosage.
4. Think about drugs that cause hypoglycemia!
   a. In particular, persons with diabetes who become intoxicated may develop life-threatening hypoglycemia due to the synergy of ethanol and insulin.
5. A patient should not be discharged until a cause is identified and/or an appropriate follow-up plan is formulated.
6. Hypoglycemia after gastric bypass requires detailed investigation.
7. Measure urinary ketones!
   a. The presence of urinary ketones in a hypoglycemic patient generally excludes hyperinsulinemia as the cause of the low glucose concentration.
8. Beware of recurrent hypoglycemia!
9. Many sulfonylurea-class oral hypoglycemic agents have very long duration of action. Prolonged treatment is often required in cases of sulfonylurea overdose.

10. Be alert for "hypoglycemia unawareness"!
    a. Patients with diabetes may fail to perceive the symptoms of hypoglycemia.
    b. Exacerbated by frequent hypoglycemic episodes and medicines that interfere with recovery (e.g., beta-blockers).
    c. In long-standing diabetes, there is blunting of counterregulation and increased sensitivity to fast-acting insulins (and therefore become hypoglycemic rapidly).

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SECTION 9

Hematologic Problems in the Intensive Care Unit

Patrick F. Fogarty

88

Disorders of Hemostasis

Adam Cuker and Suman L. Sood

I. THE BLEEDING PATIENT: GENERAL PRINCIPLES

A. Etiology.

1. Bleeding disorders (Table 88-1) may be secondary to the following:
   - **a.** Defects in the activity of platelets.
   - **b.** Defects in the activity of one or more coagulation factors (coagulopathy).
   - **c.** Congenital causes.
   - **d.** Acquired causes.
2. Hematology consultation is often necessary if the cause of bleeding is not immediately apparent and/or if specialized laboratory testing is required for diagnosis.

B. Diagnosis.

1. Clinical presentation.
   - **a.** Identify the site of bleeding.
     - **i.** Platelet disorders tend to cause mucocutaneous bleeding (e.g., epistaxis, oral, gastrointestinal [GI], genitourinary, ecchymosis).
     - **ii.** Coagulopathies (i.e., deficiencies in the activity of coagulation factors) tend to cause deep soft tissue bleeding (e.g., into joints and muscles).
     - **iii.** Bleeding from a single site (e.g., a surgical site, GI tract) warrants evaluation for an anatomic cause of bleeding.

TABLE 88-1 Selected Congenital and Acquired Bleeding Disorders

Mechanism	Congenital	Acquired
Defects in platelet activity[a]	Qualitative platelet disorders von Willebrand disease[b]	Medications Renal disease Myelodysplasia Myeloproliferative disorders
Defects in coagulation	Hemophilia A Hemophilia B Other factor deficiencies	Vitamin K deficiency Liver disease Exposure to anticoagulants DIC Trauma Acquired factor inhibitors

[a]For defects in platelet function due to thrombocytopenia, see Chapter 89.
[b]Deficiency of von Willebrand factor leads to reduced binding of platelets to sites of vascular injury and to one another.
DIC, disseminated intravascular coagulation.

b. Obtain the personal and family bleeding history.
  i. Congenital disorders: life-long history of bleeding, positive family history. Exceptions are possible (e.g., mild hemophilia).
  ii. Acquired disorders: often no previous history of bleeding, no family history.
c. Perform a careful physical examination.
  i. Skin: ecchymosis, petechiae, or nonpalpable purpura.
  ii. Hemarthrosis: warm, swollen joints.
  iii. Mucosal surface abnormalities (e.g., nasal or oral pharyngeal mucosa).

2. Perform tiered laboratory evaluation.
a. Initial testing.
  i. Complete blood count (exclude thrombocytopenia, assess for anemia).
  ii. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) (to exclude coagulopathy; see Figure 88-1 and Table 88-2).
    (a) Prolonged PT may indicate defect in tissue injury (also known as *extrinsic*) pathway of coagulation.
    (b) Prolonged aPTT may indicate defect in contact (also known as *intrinsic*) pathway of coagulation.
    (c) Prolonged PT and aPTT may indicate single defect in common pathway of coagulation or multiple defects.

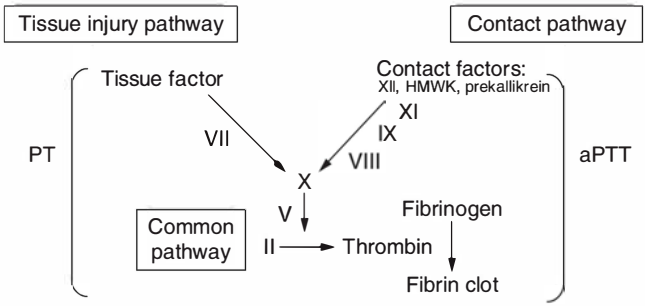

Figure 88-1. The coagulation cascade may not fully represent the process of coagulation in vivo, where activation of coagulation usually is initiated through the tissue injury (also known as *extrinsic*) pathway of coagulation, which subsequently can activate the contact (also known as *intrinsic*) pathway through thrombin-mediated activation of factors VIII and XI (not shown). The tissue injury system involves binding of activated factor VII to tissue factor and activation of factor X, whereas the contact system involves activation of factor XI by contact factors such as factor XII and subsequent activation of factor IX, which in conjunction with activated factor VIII subsequently activates factor X. The common pathway involves the activated factor X–mediated cleavage of factor II to yield thrombin, which cleaves fibrinogen to form fibrin clot. The fibrin clot is strengthened through the cross-linking action of factor XIII (not shown). aPTT, activated partial thromboplastin time; PT, prothrombin time.

TABLE 88-2 **Selected Causes of a Prolonged Activated Partial Thromboplastin Time (aPTT) and/or Prothrombin Time (PT)[a]**

Isolated prolonged aPTT	Isolated prolonged PT	Prolonged aPTT and PT
Heparin exposure	Warfarin exposure	DIC
Lupus anticoagulant[b]	Vitamin K deficiency	Liver synthetic dysfunction
Deficiency (or inhibitor) of factors VIII, IX, or XI	Liver synthetic dysfunction	Supratherapeutic warfarin or heparin
Deficiency of contact factors (XII, HMWK, or prekallikrein)[b]	Congenital deficiency of factor VII	Exposure to direct thrombin inhibitors (argatroban, dabigatran)
von Willebrand disease[c]	Mild DIC	Congential deficiency of factors II, V, or X
		Hypo- or dysfibrinogenemia
		Superwarfarin exposure[d]
		Vitamin K deficiency
		Exposure to FXa inhibitors (rivaroxaban, apixaban)[e]

[a]Bleeding disorders that typically do not feature a prolongation in the aPTT or PT include, but are not limited to, platelet function disorders, von Willebrand disease, FXIII deficiency, antiplasmin or plasminogen activator inhibtor-1 deficiency, and disorders of the vasculature or integument (e.g., Ehlers-Danlos, Osler-Weber-Rendu, scurvy).
[b]Not associated with bleeding.
[c]VWD (especially type 1) also may feature a normal aPTT.
[d]Superwarfarin pesticides include brodifacoum, bromodiolone, coumafuryl, and difenacoum.
DIC, disseminated intravascular coagulation; HMWK, high molecular weight kininogen.
[e]May not prolong PT and APTT.

b. Specialized testing.
  i. Mixing study (1:1 mix of patient and normal plasma) to detect when an inhibitior may be present.
    (a) Indication: prolonged PT or aPTT.
    (b) If prolongation completely corrects with mixing → suggests factor deficiency.
    (c) If prolongation does not completely correct with mixing → suggests that an inhibitor is present (either specific to an individual coagulation factor or nonspecific, such as a lupus anticoagulant).
  ii. Measurement of individual coagulation factor levels.
    (a) aPTT prolongation: request factors VIII, IX, and XI.
    (b) PT prolongation: request factors II, V, VII, X, and fibrinogen.
    (c) von Willebrand factor (VWF) levels.
    (d) Platelet function studies.
    (e) FXIII levels.

II. ACQUIRED DISORDERS OF HEMOSTASIS

A. Antithrombotic therapy induced.

1. General Principles.
a. The medication administration history can suggest bleeding due to anticoagulant and antiplatelet agents that is common in the ICU. See chapter 90 on Antithrombotic therapy in critically ill patients.

B. Vitamin K deficiency.

1. Pathophysiology.
a. Inadequate dietary intake of vitamin K.
b. Malabsorption of fat-soluble dietary vitamin K.
c. Decreased production of vitamin K by intestinal flora (which may be destroyed by antibiotics).

2. Diagnosis.
a. Prolonged PT (corrects with mixing).
b. Decreased levels of vitamin K–dependent clotting factors (II, VII, IX, and X).

3. Treatment.
a. Phytonadione (vitamin K_1) administration.
b. May be given PO or IV at a dose of 1 to 10 mg/day.
  i. IV dosing associated with small risk of anaphylaxis.
    (a) Administer over 30 minutes with close monitoring.
    (b) Smaller doses (e.g., 1 mg) advised.
  ii. SC dosing is discouraged due to erratic absorption.
c. Treatment may be given empirically without confirmatory laboratory studies.
  i. PT should begin to normalize within several hours of IV administration of vitamin K_1.

C. Coagulopathy of liver disease.

1. **Pathophysiology.**
   - **a.** Deficiency of hepatically synthesized clotting factors including the vitamin K–dependent factors (II, VII, IX, and X) and factors V, XI, XII, and fibrinogen.
   - **b.** Owing to any cause of liver disease that impairs synthetic function.
2. **Diagnosis.**
   - **a.** Prolonged PT ± prolonged aPTT.
   - **b.** Decreased levels of fibrinogen, factors II, V, VII, IX, X, XI, and XII.
     - **i.** Factor VIII, which is not produced in hepatocytes, is typically normal or elevated.
   - **c.** Other laboratory evidence of liver disease (e.g., decreased albumin, elevated alanine aminotransferase/aspartate aminotransferase).
3. **Treatment.**
   - **a.** Blood products.
     - **i.** Should be administered only if bleeding, at high risk of bleeding, or when an invasive procedure is planned.
     - **ii.** Isolated mildly–moderately prolonged clotting times without bleeding not sufficient grounds for treatment.
     - **iii.** Ongoing treatment may be required until liver synthetic deficiency is resolved (e.g., by definitive treatment, such as liver transplantation, or recovery following shock liver).
   - **b.** Fresh frozen plasma (FFP).
     - **i.** Usual dose: infusions of approximately 10 to 15 mL/kg (usually 3 to 5 250 mL units).
     - **ii.** Severe hepatic failure and ongoing bleeding: consider continuous infusion (FFP drip).
     - **iii.** Goal: cessation in bleeding.
       - **(a)** A target INR of ≤1.5 is often cited but may be difficult to achieve.
     - **iv.** Be alert for signs of volume overload.
   - **c.** Cryoprecipitate.
     - **i.** Usual dose: 10 units per infusion is expected to increase fibrinogen levels by 50 mg/dL.
       - **(a)** Goal: cessation in bleeding and/or fibrinogen of ≥80 to 100 mg/dL.
   - **d.** Follow aPTT, PT, fibrinogen, and complete blood count every 4 to 8 hours if actively bleeding.

D. Disseminated intravascular coagulation (DIC).

1. **Pathophysiology.**
   - **a.** Uncontrolled activation of coagulation, which paradoxically may lead to bleeding due to consumptive deficiencies of multiple clotting factors and platelets.
2. **Etiology.**
   - **a.** Infection/sepsis.
   - **b.** Malignancy (e.g., acute promyelocytic leukemia, Trousseau syndrome).

c. Obstetrical complications (e.g., placental abruption; hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome; amniotic fluid embolism).
d. Tissue damage (e.g., trauma, burns).
e. Vascular abnormalities (e.g., abdominal aortic aneurysm, giant hemangioma).
f. Toxic procoagulant molecules (e.g., snake bite).
g. Fat embolism (e.g., fracture of long bones, sickle cell crisis).

3. Diagnosis.
a. Presence of an underlying etiology.
b. Laboratory testing.
i. Decreased fibrinogen (due to consumption).
ii. PT/aPTT may be prolonged (due to consumption of clotting factors).
iii. Thrombocytopenia may be present (due to accelerated platelet consumption).
iv. Increased D-dimer, a measure of cross-linked fibrin degradation products (due to accelerated fibrin degradation).
v. Red blood cell fragments (schistocytes) may be present on blood smear.

4. Treatment.
a. Treatment of the underlying cause (e.g., antibiotics for sepsis, delivery for pregnancy related).
b. Hemostatic therapy (for dosing, see Table 88-3).

TABLE 88-3 Management of Disseminated Intravascular Coagulation (DIC): Blood Products[a]

Component	Typical dose	Associated laboratory parameter[b]	Target laboratory parameter	
			No clinically significant bleeding	Clinically significant bleeding
Platelets	1 dose[c]	Platelet count	>10 K/μL	>20–50 K/μL
Cryoprecipitate	10 units	Fibrinogen	>80–100 mg/dL	>80–100 mg/dL
FFP	3–5 units	aPTT/PT	–	≤1.5 × upper limit normal reference range

[a]Transfuse blood products only if clinically significant bleeding or high risk of bleeding.
[b]Before transfusion, establish baseline platelet count, PT, aPTT, D-dimer, and fibrinogen. Follow laboratory parameters every 4–6 h until DIC resolves and underlying condition successfully treated.
[c]One dose of platelets is equal to 1 unit of single-donor platelets or a four or six pack of pooled random donor platelets.
FFP, fresh frozen plasma; aPTT, activated partial thromboplastin time; PT, prothrombin time.

i. Should be given only to patients with high risk for bleeding, with clinically significant bleeding, or in need of invasive procedures.
   (a) Platelet transfusion.
   (b) Cryoprecipitate.
   (c) FFP.
   (d) Coagulation tests (PT, aPTT, fibrinogen, platelet count) should be monitored frequently to assess response to hemostatic therapy.
ii. For refractory bleeding (e.g., mucocutaneous oozing, ongoing bleeding from catheter exit sites) despite above measures, consider low-dose heparin.
   (a) Typical dose: 5 to 10 units/kg/h (*no* bolus).
   (b) Avoid in intracranial/GI bleeding, placental abruption, and imminent surgery.

E. Trauma-induced coagulopathy.

1. **Pathophysiology.**
   a. Major contributor is massive volume resuscitation with fluids or packed red blood cells (PRBCs), which are deficient in clotting factors and platelets, leading to dilutional thrombocytopenia and coagulopathy.
   b. Other possible contributing factors.
      i. Acidemia (impairs activity of clotting cascade).
      ii. Hypocalcemia (impairs activity of calcium-dependent clotting factors).
      iii. Hypothermia (impairs platelet function).
      iv. Concurrent DIC.
2. **Diagnosis.**
   a. Clinical presentation.
      i. Persistent bleeding from mucosal and serosal surfaces and wound and vascular access sites following major trauma.
   b. Thrombocytopenia.
   c. Prolonged PT and aPTT (correct with mixing; deficiency of multiple clotting factors can be demonstrated but is rarely necessary).
   d. Hypofibrinogenemia.
3. **Treatment.**
   a. Liberal transfusion of platelets, FFP, and cryoprecipitate.
      i. Goals: aPTT/PT ≤1.5 × upper limit of normal; fibrinogen ≥100 mg/dL; platelets >50,000/μL.
   b. Body and fluid warming to treat hypothermia.
   c. Correction of electrolyte and acid–base disturbances.
   d. Consider tranexamic acid, recombinant factor VIIa (rhFVIIa), or prothrombin complex concentrate in otherwise uncontrolled bleeding (further studies warranted).

F. Acquired hemophilia.

1. **Pathophysiology.**
   a. Neutralizing autoantibodies against endogenous coagulation factor VIII.

2. **Etiology.**
   - **a.** Malignancy.
   - **b.** Autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus).
   - **c.** Postpartum state.
   - **d.** Idiopathic (50% of cases).
3. **Diagnosis.**
   - **a.** Prolonged aPTT (does not correct with mixing).
   - **b.** Low or unmeasurable factor VIII activity level.
   - **c.** Inhibitor titer using the Bethesda assay; reported in Bethesda units (B.U.).
4. **Treatment.**
   - **a.** Control of bleeding.
     - **i.** Low-titer inhibitors (<5 B.U.): give high doses of factor VIII concentrate.
     - **ii.** High-titer inhibitors (≥5 B.U.) or severe bleeding: give inhibitor-bypassing agent (Table 88-4).
       - **(a)** Activated prothrombin complex concentrates (aPCCs) (e.g., Factor VIII Inhibitor Bypassing Activity [FEIBA]): 50 to 100 units/kg IV every 8 to 12 hours initially.
       - **(b)** rhFVIIa: 90 μg/kg IV every 2 hours initially.
   - **b.** Inhibitor eradication.
     - **i.** Prednisone (typically 1 mg/kg/day PO) initially.
     - **ii.** Cyclophosphamide (typically 2 mg/kg orally) or rituximab (typically 375 mg/m^2 IV weekly × 4 weeks) is added if inhibitor persists after 3 weeks of prednisone.
       - **(a)** Some experts advocate the initial concurrent use of prednisone and cyclophosphamide or rituximab.
       - **(b)** Third-line immunomodulatory agents: cyclosporine, azathioprine, intravenous immune globulin (IVIG).

TABLE 88-4 Bypassing Agents for the Treatment of Bleeding Due to an Inhibitor

Bypassing agent	Description	Initial dose/schedule
FEIBA	Activated prothrombin complex concentrate (plasma-derived)	50–100 international units/kg q8–12 h IV
rhFVIIa (NovoSeven)	Human activated factor VII (recombinant)	90 μg/kg q2 h IV

FEIBA, factor VIII inhibitor-bypassing activity; rhVIIa, recombinant human factor VIIa.

G. Renal failure/uremic platelets.

1. **Pathophysiology.**
   - **a.** Uremic toxins impair platelet function in some patients with kidney disease.
2. **Diagnosis.**
   - **a.** Abnormal platelet function testing (rarely necessary).
   - **b.** Note: the degree of azotemia does not correlate well with the risk of bleeding.
3. **Treatment**
   - **a.** Desmopressin acetate (DDAVP) (for dosing, see Table 88-5).
   - **b.** Correction of anemia: target hematocrit ≥30%.
     - **i.** May improve platelet function by facilitating interaction of platelets with the vessel wall.
     - **ii.** Accomplished acutely by red cell transfusion and chronically by administration of erythropoietin-stimulating agent.
     - **iii.** Hemodialysis.
     - **iv.** High-dose conjugated estrogens (for severe/refractory cases):
       - **(a)** Short-term (i.e., ≤7 days) use only.
       - **(b)** Typically 50 mg PO daily.
     - **v.** Cryoprecipitate.

H. Myeloproliferative disorders (MPDs)/myelodysplastic syndrome (MDS).

1. **Pathophysiology.**
   - **a.** MPDs and MDS may lead to production of abnormal blood cells, including platelets.
2. **Diagnosis.**
   - **a.** Laboratory evidence of MPDs or MDS (e.g., abnormal blood cell counts, abnormal blood cell morphology on blood smear or bone marrow examination, and/or genetic mutations or karyotypic abnormalities).
   - **b.** Platelet function testing may be required to establish a qualitative defect, as distinguished from decreased platelet function due to thrombocytopenia (as commonly occurs in MDS and spent-phase MPD).
3. **Treatment.**
   - **a.** Treat underlying disorder.
   - **b.** Consider platelet transfusions for clinically significant bleeding.

III. CONGENITAL DISORDERS OF HEMOSTASIS

A. Hemophilia.

1. Pathophysiology.
   - **a.** Congenital deficiency of a coagulation factor due to a mutation in the gene for factor VIII (hemophilia A) or factor IX (hemophilia B).
   - **b.** X-linked inheritance.

TABLE 88-5 Treatment of von Willebrand Disease

Agent	Mechanism	Dose/frequency	Comments
DDAVP	Releases VWF and FVIII from endothelial cells into circulation	0.3 μg/kg in 50 mL normal saline (NS) IV[a] over 20 min; may repeat in 12–24 h, maximum 2–3 doses	Fluid restrict (≤750 mL in the 24 h after dosing) and limit doses to reduce risk of hyponatremia. Tachyphylaxis occurs after 2–3 doses.
VWF-containing factor VIII concentrate (Humate-P, Alphanate, Wilate)	Direct replacement of deficient VWF and factor VIII activity	For major bleeding or procedures: 40–80 RCoF[b] units/kg IV bolus q12 h initially followed by 20–60 RCoF units/kg q12 h once hemostasis has been established.	Goal VWF and FVIII levels are >80%–100% for major bleeding or procedures. Trough levels should be performed to ensure adequate dosing.
ε-aminocaproic acid (Amicar)	Inhibits fibrinolysis	IV: 5 g (in 250 mL NS) bolus followed by 1 g/h continuous infusion Oral: 4–6 g q4–6 h Max. dose (IV or PO) is 24 g/24 h	For VWD, adjunctive to either DDAVP- or VWF-containing factor VIII concentrate for treatment of mucosal bleeding. Avoid if active hematuria, DIC.
Tranexamic acid	Inhibits fibrinolysis	1,300 mg PO TID for a maximum of 5 days	FDA-approved for treatment of heavy menstrual bleeding. Avoid if active hematuria, DIC.

[a]Intranasal formulation (Stimate) also available; dose for adults weighing >50 kg is 150 μg (one spray) in *each* nostril.
[b]RCoF, Ristocetin cofactor, a measure of VWF activity.
DDAVP, desmopressin acetate; VWF, von Willebrand factor; RCoF, ristocetin cofactor; VWD, von Willebrand disease; DIC, disseminated intravascular coagulation.

TABLE 88-6 Bleeding Phenotypes in Hemophilia by Factor Level

Severity of hemophilia	Factor level	Usual manifestation of bleeding
Severe	<1%	Spontaneous; often manifests in infancy/childhood
Moderate	1%–5%	Spontaneous or trauma induced
Mild	5%–20%	Trauma induced only

i. Males only affected.
   (a) Family history usually shows affected males, but some patients are affected by de novo mutations, leading to negative family history.
ii. Females typically are asymptomatic carriers.
   (a) Owing to variable lyonization, some females are symptomatic carriers.

2. Clinical presentation.
   a. Bleeding phenotype determined by the level of residual clotting factor activity (Table 88-6).
   b. Bleeding into soft tissues (joints and muscles) is most common.
      i. Bleeding at any site, however, is possible.
      ii. Bleeding may be life threatening or limb threatening (Table 88-7).
3. Diagnosis.
   a. Laboratory studies.
      i. Prolonged aPTT (corrects with mixing).
      ii. Reduced or unmeasurable activity level of factor VIII (hemophilia A) or factor IX (hemophilia B).

TABLE 88-7 Limb- or Life-Threatening Bleeding Syndromes in Hemophilia

Site	Clinical presentation	Diagnostic testing
Intracranial	Head trauma, severe headache, mental status changes	Stat head CT
Retroperitoneal	New back pain	Stat CT of abdomen/pelvis
Retropharyngeal	Stridor	Lateral x-ray of neck, ENT evaluation
Compartment syndrome	Recent intramuscular bleed; disproportionate pain, neurovascular findings	Serial neurovascular examinations, vascular surgery evaluation, ultrasound, CT/MRI

CT, computed tomography; ENT, ear nose throat; MRI, magnetic resonance imaging.

4. Treatment (Table 88-8).
   a. If clinical suspicion for limb- or life-threatening bleeding, administer factor before completing radiographic/diagnostic work-up.
   b. Factor VIII and IX concentrates.
      i. Contain much higher concentrations of factor than FFP or cryoprecipitate (use of both should be avoided if possible due to large volume required and lack of viral inactivation).
      ii. Both plasma-derived and recombinant products available.
      iii. Administered by IV push (Table 88-8).
   c. DDAVP (for dosing, see Table 88-5).
      i. Effective in some cases of mild hemophilia A only.
   d. Antifibrinolytic agents: ε-aminocaproic acid and tranexamic acid (for dosing, see Table 88-5).
      i. Useful for mucosal bleeding or procedures involving mucosa.
   e. Transfusion of PRBCs (if anemic).
5. Complications.
   a. Inhibitor formation.
      i. Alloantibody directed against deficient coagulation factor.
      ii. Occurs in 25% of patients with severe hemophilia A; less common in hemophilia B and mild/moderate hemophilia A.

TABLE 88-8 Treatment of Bleeding in Hemophilia

Disorder	Subtype	Treatment for minor bleeding[a]	Treatment for major bleeding[b]	Treatment periprocedurally
Hemophilia A	Mild	DDAVP[c] or FVIII 25 units/kg initially[d]	FVIII concentrate, 50 units/kg IV initially[e]	DDAVP[c], or FVIII concentrate, 50 units/kg IV pre-op[e]
	Moderate/ severe	FVIII concentrate: 25 units/kg IV initially[d]	FVIII concentrate, 50 units/kg IV initially[e]	FVIII concentrate, 50 units/kg IV pre-op[e]
Hemophilia B	Any	FIX concentrate, 50–60 units/ kg IV initially[e]	FIX concentrate, 100–120 units/kg IV initially[e]	FIX concentrate, 100–120 units/kg IV pre-op[e]

[a]For example, typical hemarthrosis or intramuscular hemorrhage, epistaxis.
[b]For example, intracranial, retroperitonal, or GI bleeding.
[c]For dose of DDAVP, see Table 88-8.
[d]May repeat in 12 to 24 h if ongoing symptoms.
[e]Follow initial dose with 25 units/kg (FVIII concentrate) or 50 to 60 units/kg (FIX concentrate) IV every 8 to 12 h to maintain factor activity ≥50% for 3 to 10 d or as long as bleeding is present. Consider adjunctive ε-aminocaproic acid for mucosal bleeding or procedures involving mucosa. Less-invasive procedures (e.g., endoscopy with biopsy) may require less intensive factor replacement.
DDAVP, desmopressin acetate.

iii. Causes bleeding and poor response to infusion of factor concentrate.
iv. Treatment.
(a) Low-titer inhibitors (<5 B.U.): may be overcome by high doses of factor concentrate.
(b) High-titer inhibitors: treat with agents that bypass the inhibitor (Table 88-4).

b. Blood-borne viral infection.
i. High rate of infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) acquired through tainted blood products in 1970s and 1980s.
ii. Currently available factor products in developed countries undergo viral inactivation that greatly reduces infection risk or are recombinant.

c. Hemophilic arthropathy.
i. Chronic joint damage due to recurrent hemarthroses.

B. von Willebrand disease (VWD).

1. Pathophysiology.
a. Deficiency or dysfunction of VWF.
b. Normal function of VWF.
i. Tethers platelets to the subendothelium.
ii. Bridges platelets and links them to the fibrin clot.
iii. Serves as a carrier for factor VIII, protecting it from accelerated clearance.

2. Epidemiology.
a. Most common congenital bleeding disorder.

3. Classification.
a. Type 1 (70% to 80% of cases): mild-to-moderate quantitative deficiency of VWF.
b. Type 2 (20% to 30% of cases): functional (qualitative) deficiency of VWF.
c. Type 3 (rare): severe quantitative deficiency of VWF.

4. Diagnosis.
a. Decreased VWF antigen.
b. Decreased VWF activity.
i. Usually measured by ristocetin cofactor assay.
c. Decreased factor VIII activity.
i. aPTT may be prolonged if factor VIII activity sufficiently decreased, but frequently is normal.
d. VWF multimer electrophoresis can help distinguish among types.

5. Treatment (Table 88-5).
a. DDAVP.
i. Synthetic analog of vasopressin.
ii. Primarily effective in type 1 VWD, some type 2 VWD.
(a) Patients should have previously undergone therapeutic challenge to assess responsiveness.

(b) If not previously performed or data unavailable, must measure postinfusion VWF and factor VIII activities to ensure hemostatic levels, or administer VWF-containing factor VIII concentrate (see below) instead of DDAVP.

iii. May worsen thrombocytopenia in patients with type 2B VWD.

b. VWF-containing factor VIII concentrate.

c. Antifibrinolytic agents: ε-aminocaproic acid and tranexamic acid.

i. Primarily adjunctive.

ii. Useful for mucosal bleeding or invasive procedures involving the mucosa.

iii. Tranexamic acid is FDA approved for treatment of heavy menstrual bleeding.

C. Congenital qualitative platelet disorders.

1. Pathophysiology.
   a. Mutations in genes encoding proteins responsible for platelet activation, aggregation, or secretion.
   b. Poorly defined in most cases.
2. Specific disorders.
   a. Bernard-Soulier: very rare, autosomal recessive; deficiency of the VWF-binding site on platelets.
   b. Glanzmann thrombasthenia: very rare, autosomal recessive; deficiency of the fibrinogen-binding site on platelets.
   c. Storage pool disorders: rare, heterogeneous group of disorders with deficient or abnormal platelet granules.
   d. Others (e.g., defects of platelet signaling; more common).
3. Diagnosis.
   a. Abnormal platelet aggregation studies or platelet function analyzer (PFA-100) results.
4. Treatment (if clinically significant bleeding or requirement for invasive procedure).
   a. DDAVP (for dosing, see Table 88-5).
   b. Antifibrinolytic agents: ε-aminocaproic acid and tranexamic acid (for dosing, see Table 88-5).
   c. Platelet transfusion.
   d. rhVIIa (NovoSeven) may be useful in patients with Glanzmann thrombasthenia.

D. Other coagulation factor deficiencies.

1. Pathophysiology.
   a. Mostly autosomal recessive inheritance.
2. Incidence: very rare.
3. Treatment.
   a. Deficiencies of factors II, V, X, and XI usually treated with infusion of FFP.
      i. Platelet transfusion may also be used to treat factor V deficiency if refractory bleeding.
      ii. PCC may be used to treat deficiencies of factor II or factor X.

b. Deficiency of fibrinogen usually treated with cryoprecipitate or fibrinogen concentrate.
c. Deficiency of factor VII usually treated with rhVIIa.
d. Deficiency of factor XIII usually treated with cryoprecipitate of factor XIII concentrate.

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89 Thrombocytopenia in the Critical Care Patient

Terry B. Gernsheimer

I. GENERAL PRINCIPLES

A. Definition.

1. Less than 150,000/μL, generally not clinically significant until <100,000/μL.
2. Relative—an acute drop from a higher platelet count may be pathologic.

B. Pathophysiology.

1. Decreased production.
2. Increased destruction, consumption.
3. Increased sequestration in enlarged spleen.
4. Dilutional—effect of massive transfusion and fluid resuscitation.
5. States with multiple causes of thrombocytopenia.
   a. Cirrhosis with portal hypertension.
   b. Hepatitis.
   c. Human immunodeficiency virus (HIV).
   d. Other viral illnesses.
   e. Patients with multiple medical problems on multiple drugs.

C. Diagnosis.

1. Complete blood count with peripheral smear examination.
   a. Rule out pseudothrombocytopenia due to platelet clumping.
   b. Review for erythrocyte abnormalities: schistocytes, teardrops, nucleated red blood cells.
   c. Review for white blood cell abnormalities: immature or dysplastic forms.
2. Coagulation testing.
   a. Identify associated coagulation abnormalities.
3. Additional blood tests.
   a. Viral titers and antibody (e.g., HIV, hepatitis C [HCV] infection).
   b. Autoimmune disorders—antibody testing.
   c. Other—see specific disorders.
4. Radiologic.
   a. Abdominal ultrasound—evaluation of spleen size.
   b. CT scanning—evaluation for lymphoproliferative disease.

TABLE 89-1 Target Platelet Count Values in Selected Clinical Scenarios[a]

Platelet count (×10⁹/L)	Clinical scenario
>10	Prevention of spontaneous bleeding in critically ill patient
>20–50	Insertion of central venous catheters[b]
>30–50	Administration of therapeutic anticoagulation
>30–50	Secondary prevention of serious bleeding (e.g., gastrointestinal) due to severe thrombocytopenia
>30–50	Minor surgery and some invasive procedures[c]
>50–100	Major surgery
>100	Secondary prevention of intracranial hemorrhage, microvascular bleeding

[a]The values provided are suggestions only; management must be individualized with respect to the underlying cause of thrombocytopenia, presence of bleeding, and other relevant clinical factors.
[b]Nontunneled catheters may be inserted with platelet counts in the lower end of the specified range.
[c]Representative procedures include needle biopsies and endoscopy with biopsy; skin biopsy and bone marrow biopsy typically may be performed at lower platelet counts than the specified range.

5. Bone marrow examination indications.
   a. Unclear pathophysiology.
   b. Multiple cytopenias.
   c. Suspected infiltrative process.

D. Therapy (Table 89-1).

1. Indications for platelet transfusion.
   a. Bleeding or necessary invasive procedures.
   b. Prophylactic—very severe (<10,000/μL) thrombocytopenia or <20,000 when fever or mucositis are present.
   c. Other blood components as indicated to correct coagulation abnormalities or severe anemia.
   d. Relative contraindications to platelet transfusion.
      i. Thrombotic thrombocytopenic purpura (TTP) unless bleeding is present—worsened thrombotic tendency reported.
      ii. Immune thrombocytopenia unless bleeding present—poor or short-lived response.
      iii. Heparin-induced thrombocytopenia (HIT) without bleeding—unknown.
2. Nonspecific therapy for bleeding.
   a. Antifibrinolytic agents—Epsilon-aminocaproic acid, tranexamic acid.
   b. Recombinant factor VIIa (Novo Seven)—unproven and controversial. May be indicated in acute intracranial, other life-threatening bleeding in patients without response to platelet transfusion.
3. Secondary thrombocytopenias—direct therapy at underlying cause(s).
4. Primary thrombocytopenia—depends on specific disorder.

II. DECREASED PLATELET PRODUCTION

A. Isolated thrombocytopenia.

1. Drugs, ETOH, viral (e.g., HIV, HCV).
2. Decreased thrombopoietin—liver disease.
3. Amegakaryocytic thrombocytopenia.

B. Multiple cytopenias.

1. Marrow toxins.
   a. Drugs, alcohol, radiation.
2. Nutritional—for example, B_{12} and/or folate deficiency.
3. Metabolic—for example, thyroid disorders.
4. Primary marrow disorders.
5. Hematopoietic stem cell disorders.
   a. Marrow infiltration.
6. Hemophagocytic syndrome.

C. Diagnosis.

1. Peripheral blood smear.
   a. Bizarre forms—for example, abnormal granulation suggests myelodysplasia.
   b. Red blood cell abnormalities.
      i. Teardrops, nucleated red blood cells—suggest marrow infiltrative diseases.
      ii. Macrocytosis—B_{12} or folate deficiency, myelodysplasia.
   c. White blood cell abnormalities.
      i. Immature forms—suggest leukemia.
      ii. Multilobed neutrophils, bizarre forms—B_{12} or folate deficiency, myelodysplasia.

D. Therapy.

1. Direct at underlying or associated disorder.

III. INCREASED SPLENIC SEQUESTRATION

A. Etiology.

1. Portal hypertension.
2. Myeloproliferative disease.
3. Lymphoma.
4. Storage and infiltrative diseases of the spleen.
5. Chronic hemolysis.
6. Granulomatoses—for example, tuberculosis, sarcoidosis.

B. Diagnosis.

1. Imaging—abdominal ultrasound, CT.
2. Biopsy of apparently pathologic tissue, bone marrow.

C. Treatment.

1. Direct at underlying cause.

IV. DISORDERS OF INCREASED PLATELET DESTRUCTION

- **A.** Characterized by shortened platelet life span (normal 7 to 10 days).
- **B.** Nonimmune—isolated or combined platelet consumption.
- **C.** Autoimmune.
- **D.** Alloimmune.

V. AUTOIMMUNE THROMBOCYTOPENIAS

- **A.** Etiology.
  1. Primary—immune thrombocytopenic purpura (ITP).
  2. Secondary.
     - **a.** Associated with other autoimmune disease, for example, systemic lupus.
     - **b.** Associated with malignancy (e.g., lymphoproliferative disease).
     - **c.** Complication of infection with HIV, HCV, hepatitis B virus (HBV), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and others.
     - **d.** Drug associated.

VI. ITP

- **A.** General principles.
  1. Acute ITP may present with any severity of thrombocytopenia.
  2. Initial presentation frequently abrupt in onset.
  3. Petechiae, bruising, mucosal bleeding—most common manifestations.
- **B.** Epidemiology.
  1. Adults—85% chronic relapsing disorder.
  2. Children—90% acute, self-resolving disorder.
  3. Female predominance (F:M = 3:2) except in children, elderly.
- **C.** Etiology.
  1. Idiopathic, may present following acute viral illness.
  2. Secondary ITP may be initial presentation of connective tissue disease, lymphoproliferative malignancy, HIV infection.
  3. May be associated with antiphospholipid antibody syndrome.
- **D.** Pathophysiology.
  1. Antibody against glycoproteins on the platelet membrane.
  2. Reticuloendothelial, especially splenic, platelet clearance.
  3. Inadequate platelet production response.
  4. Direct T-cell toxicity may play a part.
- **E.** Diagnosis.
  1. Diagnosis of exclusion.
  2. Clinical—presentation, therapeutic response.
  3. Laboratory testing.
     - **a.** Other peripheral blood and hemostatic measurements normal unless the patient has been bleeding.

b. Rule out associated disorders when indicated by history or clinical presentation.
c. Antiplatelet antibodies generally not helpful in diagnosis.
d. Bone marrow examination not required unless diagnosis uncertain or patient older than 60 years.
i. Normal-to-increased numbers of megakaryocytes without other abnormalities.

F. Treatment.

1. Acute.
a. Corticosteroids.
i. Usual prednisone dose 1 to 2 mg/kg.
ii. Acute emergency—up to 1 g methylprednisolone IV.
b. Immunoglobulin therapy—usually rapid response.
i. 1 to 2 g/kg IV administered over 2 to 5 days.
ii. Complications: fever, myalgias, severe headache, renal failure, aseptic meningitis, thrombosis.
Or
c. Nonsplenectomized Rh-positive patients—anti-RhD immunoglobulin (WinRho).
i. 50 to 75 μg/kg IV.
ii. Complications: fever, chills, acute intravascular hemolysis, disseminated intravascular coagulation (DIC).
d. Serious or life-threatening bleeding with severe thrombocytopenia.
i. Platelet transfusion.
(a) Markedly decrease transfused platelet survival. Transfuse only the patient with significant bleeding.
ii. Antifibrinolytic agents.
(a) Epsilon-aminocaproic acid starting dose 1 to 2 g PO/IV q6 h. Increase as needed up to 24 g total daily dose.
(b) Tranexamic acid starting dose 500 mg to 1 g IV/PO q8 h.
(c) Contraindication—urinary tract bleeding, DIC.

2. Chronic.

Options for patients who relapse after immunoglobulin therapy or prednisone taper include splenectomy, thrombopoietin-mimetic agents, pulse corticosteroids, alkylating agents, monoclonal antibody, azathioprine, and other immunosuppressive agents.

G. Complications.

1. Therapeutic complications may interfere more with quality of life and be more severe than bleeding risk in mild or moderately thrombocytopenic patients (30 to 100,000/μL).
2. Chronic steroid therapy and immunosuppression—severe osteoporosis, infections, and other complications.

H. Prognosis.

1. Severe refractory ITP: 10% to 25% risk of significant bleeding during disease course.

VII. DRUG-ASSOCIATED AUTOIMMUNE THROMBOCYTOPENIA

A. General principles.

1. Multiple drugs implicated.
2. Most common offenders: quinine and derivatives, antibiotics, thiazide diuretics, IIb/IIIa inhibitors.
3. HIT: treated differently; see below.

B. Diagnosis.

1. History of exposure to possibly offending drug.
2. Laboratory testing.
   a. Drug-dependent platelet autoantibody—limited availability.
   b. No other blood or hemostatic abnormalities identified.
3. Contraindicated: readministration of suspected drug as diagnostic challenged.

C. Therapy.

1. Discontinue suspected offending agent(s).
2. Intravenous gamma-globulin therapy: administer as for ITP.
3. Platelet transfusion may be indicated for bleeding.
4. Plasma exchange in severe refractory cases.

VIII. HIT

A. General principles.

1. Immune reaction to a heparin/Platelet Factor 4 (PF4) complex.
2. May be associated with life-threatening prothrombotic state.
3. Discontinue all heparin therapy (including low molecular weight heparin [LMWH] and heparin flushes) while considering the diagnosis.
4. Ultimately a clinical diagnosis.

B. Pathophysiology.

1. Heparin bound to PF4 immunogenic.
2. Antibodies bound to the heparin/PF4 complex cause platelet activation, aggregation, and thrombin generation.
3. Thrombin further activates platelets.
4. Large and small venous and arterial vessel thrombosis may occur.

C. Diagnosis.

1. Clinical.
   a. Exposure to any type, administration route, or dose of heparin.
      i. Unfractionated > low molecular weight.
      ii. Intravenous > subcutaneous.
   b. Onset usually 4 to 10 days after initial heparin exposure.
   c. >50% fall in platelet count more important than absolute thrombocytopenia.
   d. Post-op inflammatory state may mask a relative drop in platelet count.
   e. Suspect if new or extension of thrombus during heparin anticoagulation.
   f. 4T Score (http://www.qxmd.com/calculate-online/hematology/hit-heparin-induced-thrombocytopenia-probability): estimates clinical probability of HIT.

2. Laboratory.
   a. PF4 ELISA (enzyme-linked immunosorbent assay) sensitive, may be nonspecific.
      i. High degree of false positivity post–cardiopulmonary bypass or balloon pum.
      ii. Magnitude of optical density (OD) result predictive for HIT.
         (a) 0.4 to 0.99 OD units: ≤5% risk of HIT.
         (b) ≥2.00 OD units: approximately 90% risk of HIT.
   b. Serotonin release assay (more specific; best combined with results of immunologic assay such as PF4 ELISA; specialized laboratories only).
   c. Heparin–platelet aggregation studies (specialized laboratories only).

D. Treatment.

1. Discontinue all heparin exposure.
2. Rule out thrombosis—Doppler studies.
3. Anticoagulation with alternative anticoagulants.
   a. Direct thrombin inhibitors.
      i. No antidotes.
      ii. IV argatroban (direct thrombin inhibitor)—hepatic clearance.
      iii. IV bivalirudin (direct thrombin inhibitor)—increased half-life with renal insufficiency.
   b. SC fondaparinux (synthetic pentasaccharide)—long half-life (17 hours), not reversible; use as initial treatment controversial.
   c. Do not start Coumadin until platelet count recovery; overlap with a direct thrombin inhibitor (DTI).

E. Prognosis.

1. Associated with up to a 50% thrombosis rate, leading to serious morbidity and mortality without direct thrombin inhibitor therapy.
2. Appropriate length of ongoing anticoagulation unclear, usually ≥30 days.

IX. ALLOIMMUNE THROMBOCYTOPENIAS

A. Etiology.

1. Antibodies against foreign platelet antigens encountered through transfusion or pregnancy.

X. POSTTRANSFUSION PURPURA (PTP)

A. General principles.

1. Severe thrombocytopenia.
2. Typically occurs 5 to 10 days posttransfusion of cellular blood component.
3. Most common in multiparous women.

B. Pathophysiology.

1. Alloimmunization to foreign platelet antigen occurs through pregnancy or transfusion.
2. Allogeneic platelet destruction with recall of antibody.
3. Mechanism of associated autologous platelet destruction poorly understood.

C. Diagnosis.

1. Laboratory—strong serum antibody, IgG or IgM class, most commonly against platelet antigen PLA-1.

D. Treatment.

1. IV Immunoglobulin 1 to 2 g/kg over 2 to 5 days.
2. Plasma exchange in refractory cases.
3. Poor responses to platelet transfusion.

XI. NONIMMUNE THROMBOCYTOPENIA

A. Combined consumption (DIC).

1. Associated with fibrinogen deposition and consumption.
2. Sepsis, malignancy, obstetric complications, massive tissue injury, or snake bite.

B. Diagnosis.

1. Peripheral blood smear.
   a. Bands, toxic granulations, Dohle bodies.
   b. May see red cell fragmentation (schistocytes).
2. Abnormal coagulation tests.
   a. Increased prothrombin time (PT), partial thromboplastin time (PTT), or thrombin time.
   b. Falling fibrinogen levels.
   c. Increased D-dimer levels.

C. Treatment.

1. Directed at the underlying cause.
2. Support with transfusion therapy for bleeding.

XII. ISOLATED PLATELET CONSUMPTION

A. Vascular injury, high shear flow—vasculitis, intravascular prosthetic devices.
B. Microangiopathic hemolysis—for example, TTP, hemolytic uremic syndrome (HUS).

XIII. MICROANGIOPATHIC HEMOLYTIC ANEMIAS

A. General principles.

1. Isolated platelet consumption associated with intravascular hemolysis
2. Patients present with end-organ signs and symptoms due to microvascular thrombosis.

B. Etiology.

1. Thrombotic thrombocytopenic purpura.
2. Hemolytic uremic syndrome.
3. *Escherichia coli* 0157:H7 or *Shigella* species infection.
4. Malignant arterial hypertension.
5. Drug induced—for example, cyclosporine, mitomycin C, pentostatin, others.

6. Pregnancy.
   a. Preeclampsia.
   b. May be associated with elevated liver enzymes (hemolysis, elevated liver enzymes, and low platelet count [HELLP syndrome]).
7. HIV.

C. Diagnosis.

1. Peripheral blood smear—red cell fragmentation (schistocytes).
2. Elevated parameters of intravascular hemolysis—lactate dehydrogenase (LDH), indirect bilirubin.
3. Normal coagulation tests.

D. Treatment.

1. Discontinue offending agents.
2. Treat underlying disorder.
   a. Pregnancy associated—requires emergency delivery.
3. HUS, TTP: see Sections XIV and XV.

XIV. THROMBOTIC THROMBOCYTOPENIC PURPURA

A. General principles.

1. Acute presentation of severe-to-moderate thrombocytopenia.
2. Usually presents with fever, neurologic signs or symptoms, and/or renal abnormalities.
3. Complete pentad of signs/symptoms (i.e., microangiopathic hemolysis, thrombocytopenia, fever, neurologic and renal abnormalities) is present in fewer than 25% of cases.

B. Etiology.

1. Autoimmune.
   a. May be HIV associated.
2. Congenital.
3. Drugs, pregnancy.

C. Pathophysiology.

1. Deficiency of von Willebrand factor–cleaving enzyme (ADAMTS-13) results in persistence of large multimeric forms and increased platelet adhesion.
   a. Autoimmune: Autoantibody forms against ADAMTS-13.
   b. Congenital TTP: Familial decrease in production of functional ADAMTS-13.
2. Formation of platelet thrombi in microvasculature leads to tissue ischemia and end-organ disease.
3. Intravascular hemolysis by increased shearing forces.

D. Diagnosis.

1. Laboratory.
   a. Thrombocytopenia.
   b. Schistocytes on peripheral blood film.
   c. Elevated LDH and indirect bilirubin.

d. Hemostasis parameters otherwise normal.
e. Creatinine may be increased; hematuria may be present.
f. Usefulness of ADAMTS-13 level and antibody for diagnosis is unclear.

E. Treatment.

1. Medical emergency; >90% mortality rate without treatment.
2. Institute immediate plasma exchange; replacement fluid must be plasma.
a. Continue daily until LDH and platelet count have normalized for 2 to 3 days.
b. Some centers taper frequency before stopping.
3. Infuse plasma (4 to 6 units in adult) if plasma exchange delayed.
4. Corticosteroids—role unclear.
5. Refractory—rituximab, immunosuppression, splenectomy, or vincristine.

F. Prognosis.

1. A 90% mortality rate without rapid institution of therapy.

XV. HEMOLYTIC UREMIC SYNDROME

A. Pathophysiology.

1. Deposition of platelet thrombi in small- and medium-sized vessels.
2. No ADAMTS-13 deficiency.
3. Endemic HUS: associated with antecedent gastrointestinal illness and bacterial toxin exposure, especially in children.
4. Atypical HUS: associated with mutations in proteins that regulate complement activity (e.g., factor H).

B. Treatment.

1. Endemic cases.
a. Primarily supportive (e.g., dialysis).
b. Plasma exchange of value in some patients.
c. Majority of cases resolve with supportive care.
2. Atypical cases: may resolve following inhibition of C5 (e.g., eculizumab).

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90 Antithrombotic Therapy in Critically Ill Patients

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I. ANTIPLATELET AGENTS

A. Acetylsalicylic acid (aspirin) (Table 90-1).

1. General principles.

a. Gastrointestinal (GI) bioavailability 100%; rectal absorption is erratic (60% to 76%).

b. Aspirin is contained in many over-the-counter (OTC) products. Monitor total aspirin exposure.

c. Antiplatelet effect lasts for life span of platelet (7 to 10 days).

2. Mechanism of action.

a. Inhibits prostaglandin synthesis.

B. $P2Y_{12}$ inhibitors (Table 90-2).

1. General principles.

a. Prodrugs requiring hepatic activation.

b. Antiplatelet effect can last for life span of platelet (7 to 10 days).

2. Mechanism of action.

a. Inhibits activation of adenosine diphosphate (ADP)-mediated glycoprotein IIb/IIIa (GP IIb/IIIa) complex.

C. GP IIb/IIIa inhibitors (Table 90-3).

1. General principles.

a. Abciximab (a monoclonal antibody), eptifibatide (a heptapeptide), and tirofiban (a nonpeptide) cause competitive GP IIb/IIIa receptor blockade.

b. Duration of effect is agent specific and is influenced by its binding (i.e., abciximab irreversible up to 10 days) and renal function/elimination (i.e., for tirofiban and eptifibatide, 2 to 4 hours).

2. Mechanism of action.

a. Platelet function is inhibited by blocking the GP IIb/IIIa receptor, the major surface receptor involved in platelet aggregation.

D. Phosphodiesterase inhibitors (Table 90-4).

1. General principles.

a. Dipyridamole inhibits platelet activation and aggregation by increasing adenosine, a coronary vasodilator, and cyclic adenosine monophosphate (cAMP).

TABLE 90-1 Aspirin and Aspirin-Containing Products

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Acetylsalicylic acid (Aspirin)	Treatment of ACS +/– PCI	Loading dose: 325 mg orally 81 mg if on prior antiplatelet therapy Maintenance: 81–325 mg/d orally	• CBC • Signs of bleeding • Blood pressure • LFTs • Renal function	***Precautions*** • Thrombocytopenia • Bleeding disorders • Alcohol use (three or more drinks per day) • Pregnancy (third trimester) • GI disorders • Renal failure • Severe hepatic insufficiency • Concomitant antithrombotic medication use • Alcohol consumption ***Contraindications*** • Hypersensitivity to salicylates • Children and teenagers with chickenpox or flu symptoms (risk of Reye syndrome)
	Primary and secondary prevention of MI in patients with chronic stable angina, previous MI, or UA	81–325 mg/d orally		
	Secondary prevention in stroke and TIA patients	75–325 mg/d orally		
	Acute thrombotic stroke	160–325 mg/d, initiated within 48 h (in patients who are not candidates for thrombolytics and are not receiving systemic anticoagulation)		
	Secondary prevention in CABG, carotid endarterectomy patients	75–325 mg/d starting 6 h following procedure; if bleeding prevents administration at 6 h after CABG, initiate as soon as possible		

ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; CBC, complete blood count; LFT, liver function tests; MI, myocardial infarction; UA, unstable angina; TIA, transient ischemic attack; CABG, coronary artery bypass graft.

TABLE 90-2 $P2Y_{12}$ Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Clopidogrel (Plavix)	Treatment of ACS +/– PCI	ACS LD: 300 mg X1 PCI LD: 300–600 mg X1 Maintenance: 75 mg orally once daily	• Signs of bleeding • CBC with differential • Bleeding time • LFTs • Lipid panel (ticlopidine) • Platelet function testing may be warranted in select patients (platelet aggregometry and/or vasodilator-stimulated phosphoprotein [VASP] phosphorylation) • CYP2C19 genotyping if suspicion of poor metabolizer (clopidogrel)	***Precautions*** • Interruption of clopidogrel may cause in-stent thrombosis with subsequent fatal and nonfatal myocardial infarction • Indwelling epidural catheter • Combination of aspirin and clopidogrel in patients with recent TIA or stroke • Liver disease • Thrombotic thrombocytopenic purpura may occur (rare) • Recent trauma, surgery/biopsy, or other pathologic condition • Concomitant use with potent CYP3A inducers and inhibitors (ticagrelor) • Use of daily maintenance doses of aspirin above 100 mg not recommended (ticagrelor) • Underlying hematologic disorders • Discontinue if ANC < 1,200/mm^3 or platelet count < 80,000/mm^3 (ticlopidine) • Elevated triglycerides (ticlopidine) • Clopidogrel concentrations may be reduced in poor metabolizers of CYP2C19
	Primary and secondary prevention of MI in patients with chronic stable angina, previous MI, or UA Cerebrovascular accident Peripheral arterial occlusive disease	75 mg orally once daily		
Prasugrel (Effient)	Treatment of ACS +/– PCI	LD 60 mg X1 Maintenance: 10 mg/d orally, consider 5 mg orally once daily in patients weighing <60 kg		
Ticagrelor (Brilinta)	Treatment of ACS +/– PCI	LD 180 mg X1 Maintenance: 90 mg twice daily		

TABLE 90-2 $P2Y_{12}$ Inhibitors *(continued)*

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Ticlopidine (Ticlid)	Placement of a stent in the coronary artery Secondary prevention in thromboembolic stroke	250 mg orally twice daily		***Contraindications*** • Hypersensitivity to agent or any component of their product • Recent stroke or TIA (prasugrel) • Severe active bleeding (such as peptic ulcer or intracranial hemorrhage) • Neutropenia/thrombocytopenia • Severe liver impairment

ACS, acute coronary syndromes; LD, loading dose; PCI, percutaneous coronary intervention; CBC, complete blood count; LFT, liver function tests; MI, myocardial infarction; UA, unstable angina; TIA, transient ischemic attack; ANC, absolute neutrophil count.

TABLE 90-3 Glycoprotein IIB/IIIA Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Abciximab (Reopro)	Treatment of ACS +/– PCI	LD: 0.25 mg/kg IV bolus (over 5 min), followed by 0.125 μg/kg/min (maximum 10 μg/min) IV infusion for 12 h in combination with fibrinolytic treatment or after PCI, unless complications	• Signs of bleeding • CBC • aPTT while on heparin • ACT during PCI and prior to sheath removal • Serum creatinine	***Precautions*** • Indwelling epidural catheter • Do not remove arterial sheath unless aPTT is <45 s or ACT <150 s and heparin discontinued for 3–4 h. • Platelet count below 150,000/mm^3 • Renal insufficiency (eptifibatide and tirofiban) • Readministration of abciximab may result in hypersensitivity, thrombocytopenia, or diminished benefit due to formation of human antichimeric antibodies. • Hemorrhagic retinopathy ***Contraindications*** • Active internal bleeding • Abnormal bleeding within the previous 30 d or a history of bleeding diathesis • Concomitant or planned administration of other parenteral glycoprotein IIb/IIIa inhibitors • Hypersensitivity to active ingredient or any other product component • Hypersensitivity to murine proteins (abciximab) • Major surgery (within the previous 6 wk) • Stroke (within previous 30 d) • Severe hypertension (systolic pressure over 180–200 mm Hg or diastolic pressure above 110 mm Hg)
Eptifibatide (Integrilin)	Treatment of ACS +/– PCI	LD: 180 μg/kg IV bolus based on ABW (maximum 22.6 mg) as soon as possible, followed by 2 μg/kg ABW/min (maximum 15 mg/h) infusion until discharge or CABG surgery, up to 72 h If undergoing PCI, administer a second 180 μg/kg IV bolus 10 min after the first and continue the infusion up to discharge, or for up to 18–24 h after procedure, whichever comes first, allowing for up to 96 h of therapy Renal impairment: CrCl <50 mL/minute, 180 μg/kg actual body weight (maximum 22.6 mg) IV bolus as soon as possible, followed by 1 μg/kg/min (maximum 7.5 mg/h) infusion		

TABLE 90-3 Glycoprotein IIB/IIIA Inhibitors *(continued)*

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Tirofiban (Aggrastat)	ACS treatment	LD: 0.4 μg/kg/min IV bolus for 30 min then 0.1 μg/kg/min for 12–24 h after PCI Renal impairment: CrCl < 30 mL/minute: Load 0.2 μg/kg/min IV for 30 min then 0.05 μg/kg/min		• History or clinical suspicion of intracranial bleeding, tumor, arteriovenous malformation, or aneurysm • Pericarditis • Aortic dissection • Thrombocytopenia following prior tirofiban administration

LD, loading dose; IV, intravenous; CBC, complete blood count; ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; aPPT, activated partial thromboplastin time; ACT, activated clotting time; ABW, actual body weight; CABG, coronary artery bypass graft; CrCl, creatinine clearance.

TABLE 90-4 Phosphodiesterase Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Cilostazol (Pletal)	Intermittent claudication	100 mg orally twice daily	• Signs of bleeding • CBC • Coagulation panel • Blood pressure • Heart rate • LFTs • Signs of congestive heart failure (Cilostazol)	***Precautions*** • Hypotension • Severe coronary artery disease, abnormal cardiac rhythm • Avoid in patients with severe hepatic insufficiency (Aggrenox). • Avoid in patients with severe renal failure (Aggrenox and cilostazol). • Coagulation abnormalities ***Contraindications*** • Hypersensitivity to agent or any components of the product • CHF of any severity (cilostazol) • Hemostatic disorders or active pathologic bleeding (bleeding peptic ulcer or intracranial bleeding)
Dipyridamole (Persantine)	Thromboembolic prophylaxis after heart valve replacement	With concomitant warfarin therapy: 75–100 mg orally four times daily		
Dipyridamole extended release/aspirin (Aggrenox)	Secondary prevention in stroke and TIA patients	200 mg dipyridamole, 25 mg aspirin (one capsule) orally twice daily Patients with intolerable headache 200 mg dipyridamole, 25 mg aspirin orally daily at bedtime, with 81 mg of aspirin in the morning. Return to usual dose as soon as tolerance to headache develops (usually within a week)		

CBC, complete blood count; LFT, liver function tests; TIA, transient ischemic attack; CHF, congestive heart failure.

b. Cilostazol produces nonhomogenous vasodilation, with greater dilation in femoral beds than in vertebral, carotid, or superior mesenteric arteries, but without effect in renal arteries.

2. Mechanism of action.

a. Phosphodiesterase inhibition and suppression of cAMP degradation increase cAMP in platelets and blood vessels. This causes reversible inhibition of platelet aggregation induced by various stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress.

II. ANTICOAGULANTS

A. Unfractionated heparin (UFH) (Table 90-5).

1. General principles.

a. Glycosaminoglycan extracted from porcine intestinal mucosa.

b. Intravenous (IV) administration results in immediate onset with a $t_{1/2}$ of 60 to 90 minutes. Liver and renal disease prolonged $t_{1/2}$.

c. Subcutaneous (SC) administration delays onset of action (20 to 60 minutes).

d. Heparin resistance occurs in patients who require unusually high heparin doses (>35,000 units/day), to achieve a therapeutic-activated partial thromboplastin time (aPTT), and is attributable to antithrombin deficiency, increased heparin clearance, excess heparin-binding proteins, factor VIII, and fibrinogen (Table 90-6).

e. Heparin dosing protocols are more effective in achieving goal anticoagulation than an *ad hoc* approach.

2. Mechanism of action.

a. Combines with antithrombin to block activated factors II, IX, X, XI, and XII.

B. Low molecular weight heparin (LMWH) (Table 90-7).

1. General principles.

a. Produced from UFH, with more predictable dose response.

b. SC administration results in onset of action of 20 to 60 minutes with a $t_{1/2}$ of 3 to 6 hours.

c. Eliminated via the kidneys.

d. Dosing for obese patients is based upon adjusted body weight (AjBW).

$$\begin{aligned}&\text{AjBW} = \text{LBW} + \text{CF} \times (\text{TBW} - \text{LBW})\\&\text{CF} = \text{correction factor} = 0.4\\&\text{LBW} = (\text{height} - 150\ \text{cm}) \times 0.9 + 45\ \text{kg (female)}\ \textit{or}\ \text{LBW}\\&\qquad = (\text{height} - 150\ \text{cm}) \times 0.9 + 50\ \text{kg (male)}\end{aligned}$$

where LBW = lean body weight; TBW = total body weight; cm = centimeters.

e. Discontinuation should be considered 12 to 24 hours before procedure or surgery.

TABLE 90-5 Unfractionated Heparin

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Unfractionated heparin	VTE treatment	LD: 80 units/kg bolus 18 units/kg/h infusion adjusted per local heparin nomogram	• Signs of bleeding • CBC • aPTT: at least 4 h after initiation, then at least once daily • Anti-Xa levels (alternative if available, consider in patients with heparin resistance or antiphospholipid antibody syndromes) • HIT antibody testing (not warranted in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of immune-mediated HIT	***Precautions*** • Allergic or hypersensitivity-type reactions • Congenital or acquired bleeding disorders • Indwelling epidural catheter • GI ulceration and ongoing tube drainage of the small intestine or stomach • Hepatic disease with impaired hemostasis • Hereditary antithrombin III deficiency and concurrent use of antithrombin • Neonates and infants weighing <10 kg • Premature infants weighing <1 kg • Risk of delayed onset of HIT and HITT ***Contraindications*** • Uncontrollable active bleeding, except when due to disseminated intravascular coagulation • Instances in which blood coagulation tests cannot be performed at necessary intervals • Severe thrombocytopenia • Positive test for immune-mediated HIT • Patients within a remote history of HIT (>100 days) could be considered for a rechallenge with heparin provided a negative antibody test
	ACS treatment	LD: 60 units/kg (max 4,000 units) 12 units/kg/h (max initial dosing 1,000 units/h) +/– fibrin specific adjusted to maintain aPTT 1.5 to 2 times control or per local heparin nomogram		
	Bridge therapy for atrial fibrillation, cardioversion	IV infusion: 60–80 units/kg bolus Target aPTT, 60s (range 50–70 s)		
	Prophylaxis of VTE in the medically ill or surgical population	5,000 units SC q8 h		
	Prophylaxis of VTE in pregnancy (with prior VTE)	7,500–15,000 units SC q12 h		

VTE, venous thromboembolism; LD, loading dose; CBC, complete blood count; aPPT, activated partial thromboplastin time; ACS, acute coronary syndromes; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia with thrombosis.

TABLE 90-6 Heparin Dose Adjustment Nomogram

Variables	Adjustment
Initial dose	80 units/kg bolus, then 18 units/kg/h
aPTT < 35 s	80 units/kg bolus, then increase 4 units/kg/h
aPTT 35–45 s	40 units/kg bolus, then increase 2 units/kg/h
aPTT 46–70 s	No change
aPTT 71–90 s	Decrease infusion rate by 2 units/kg/h
aPTT > 90 s	Hold infusion 1 h, then decrease infusion rate by 3 units/kg/h

aPTT, activated partial thromboplastin time.
Adapted from Raschke R, Gollihare B, Peirce J. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. *Arch Intern Med* 1996;156: 1645–1649.

2. Mechanism of action.
   a. Inhibits both factor Xa (predominately) and factor IIa activity.

C. Factor Xa inhibitors (Table 90-8).

1. General principles.
   a. Indirect (fondaparinux) and direct (rivaroxaban and apixaban) factor Xa inhibitors.
   b. Clearance reduced in patients with renal impairment.
2. Mechanism of action.
   a. Neutralizes factor Xa, inhibiting thrombin activation and thrombus development.

D. Direct thrombin inhibitors (Table 90-9).

1. General principles.
   a. Exhibit wide variability in pharmacokinetic parameters.
2. Mechanism of action.
   a. Direct binding to thrombin, leading to inhibition of thrombin-catalyzed reactions including fibrin formation and platelet aggregation.

E. Vitamin K antagonists (VKAs) (Table 90-10).

1. General principles.
   a. Well absorbed from the GI tract and 99% bound to plasma albumin.
   b. Hepatically metabolized by cytochrome P450 (CYP) enzymes (mostly 2C9).
   c. Average half-life is approximately 40 hours but is extremely variable (range: 20 to 60 hours).
   d. Wide range of dosing required to maintain a therapeutic international normalized ratio (INR).
   e. CYP2C9 and VKORC1 genetic variation influences patient response to initial and maintenance therapy and impacts bleeding risk.
   f. Lower doses required for elderly and patients with comorbidities.
   g. Both dietary and drug interactions can influence dosing; frequent monitoring of INR may be required.

TABLE 90-7 Low Molecular Weight Heparins

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Dalteparin (Fragmin)	Treatment of VTE	<56 kg: 10,000 international units SC daily 57–68 kg: 12,500 international units SC daily 83–98 kg: 18,000 international units SC daily >99 kg: 18,000 international units SC daily	• Signs of bleeding • Anti-Xa levels in patients with significant renal impairment, those experiencing bleeding or abnormal coagulation parameters, pregnant patients, obese or low-weight patients, and children • CBC • Serum creatinine • HIT antibody testing (not warranted in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT)	***Precautions*** • Indwelling epidural catheter • Recent spinal or ophthalmologic surgery • History of recent major bleed (GI, intracranial, etc.) • Congenital or acquired bleeding disorders • Bacterial endocarditis • History of heparin-induced thrombocytopenia • Liver disease • Renal impairment (CrCl < 30 mL/min), consider UFH • Concomitant use of antithrombotic drugs • Diabetic retinopathy • Uncontrolled hypertension
	Treatment of ACS	120 international units/kg SC q12 h (Max 10,000 international units/dose)		
	Prophylaxis of VTE after hip or other major surgery (first month)	5,000 international units SC q24 h		
	Prophylaxis of VTE in the medically ill or surgical population	5,000 international units SC q24 h		

TABLE 90-7 Low Molecular Weight Heparins *(continued)*

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Enoxaparin (Lovenox)	Treatment of VTE	1 mg/kg SC q12 h OR 1.5 mg/kg SC q24 h CrCl < 30 mL/min: 1 mg/kg SC q24 h		***Contraindications*** • Severe active bleeding • Hypersensitivity to enoxaparin, dalteparin, tinzaparin, heparin, or pork products, sulfites (tinzaparin), or formulation excipients • Positive test for immune-mediated HIT • Patients within a remote history of HIT (>100 d) could be considered for a rechallenge with heparin provided a negative antibody test
	Treatment of ACS	STEMI: 30 mg bolus IV followed by 1 mg/kg SC q12 h + fibrinolytic NSTEMI/UA: 1 mg/kg SC q12 h CrCl < 30mL/min: not recommended		
	Prophylaxis/bridge therapy for atrial fibrillation/ cardioversion	1 mg/kg SC q12 h OR 1.5 mg/kg SC q24 h CrCl < 30 mL/min: 1 mg/kg SC q24 h		
	Prophylaxis of VTE in the medically ill or surgical population	40 mg SC q24 h Renal impairment: CrCl < 30 mL/min: 30 mg SC q24 h		
	Prophylaxis of VTE in trauma patients	30 mg SC q12 h OR 40 mg SC q24 h Renal impairment: CrCl < 30 mL/min: 30 mg SC q24 h		
Tinzaparin (Innohep)	Treatment of DVT	175 international units anti-Xa/kg SC daily		

VTE, venous thromboembolism; SC, subcutaneous; ACS, acute coronary syndromes; CBC, complete blood count; CrCl, creatinine clearance; HIT, heparin-induced thrombocytopenia; UFH, unfractioned heparin; STEMI, ST-segment myocardial infarction; NSTEMI, non ST-segment myocardial infarction; UA, unstable angina; DVT, deep vein thrombosis.

TABLE 90-8 Factor Xa Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Apixaban (Eliquis)	DVT prophylaxis in patients undergoing knee or hip replacement surgery Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	2.5 mg orally twice daily Initial dose 12–24 h after surgery for 10–14 d (knee) 32–38 d (hip) 5 mg orally twice daily Dose adjustments: Any two of the following (>80 y, weight < 60 kg, or serum creatinine > 1.5 mg/dL): 2.5 mg orally twice daily Renal impairment: CrCl 15–29 mL/min 2.5 mg orally twice daily CrCl < 15 mL/min or undergoing dialysis: avoid use	• Signs of bleeding • CBC • Serum creatinine • Anti-Xa levels in patients with significant renal/hepatic impairment, those experiencing bleeding or abnormal coagulation parameters, pregnant patients, obese or low-weight patients, and children (agent-specific assay calibration required)	***Precautions*** • Indwelling epidural catheter • Recent spinal or ophthalmologic surgery • History of recent major bleed • Congenital or acquired bleeding disorders • Hepatic dysfunction (apixaban and rivaroxaban) • Concomitant use with strong CYP3A4 and P-glycoprotein inhibitors and inducers (apixaban and rivaroxaban) ***Contraindications*** • Severe active bleeding • Bacterial endocarditis • Body weight <50 kg for prophylactic therapy of hip fracture, hip replacement or knee replacement surgery, or abdominal surgery; increased risk for major bleeding episodes • Fondaparinux-related thrombocytopenia • Hypersensitivity to agent or formulation excipients
Fondaparinux (Arixtra)	Treatment of VTE	<50 kg: 5.0 mg SC daily 50 to 100 kg: 7.5 mg SC daily >100 kg: 10 mg SC daily Renal impairment: consider empiric dosage reduction CrCl 50–80 mL/min: 25% reduction in total clearance CrCl 30–50 mL/min: 40% reduction in total clearance CrCl < 30 mL/min: contraindicated		

TABLE 90-8 Factor Xa Inhibitors *(continued)*

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
	Prophylaxis of VTE in major surgery and acute medically ill[a]	2.5 mg SC daily		
Rivaroxaban (Xarelto)	Prophylaxis of stroke and systemic embolism in nonvalvular atrial fibrillation	20 mg orally daily with meal Renal impairment: CrCl 15–49 mL/min: 15 mg orally daily with meal CrCl < 15 mL/min: avoid use		
	Treatment of VTE	15 mg orally twice daily for 3 wk, then 20 mg orally daily Renal impairment: CrCl < 30 mL/min: avoid use	• LFTs (apixaban and rivaroxaban)	• CrCl < 30 mL/min (fondaparinux) • Severe liver failure (apixaban) • Hepatic dysfunction with coagulopathy (rivaroxaban)
	DVT prophylaxis in patients undergoing knee or hip replacement surgery	10 mg orally daily for 5 wk (hip) 2 wk (knee) [a]First dose within 6–10 h postsurgery		

[a]Indicates off-label use of medication.
DVT, deep vein thrombosis; CBC, complete blood count; SC, subcutaneous; VTE, venous thromboembolism; CrCl, creatinine clearance; LFTs, liver function tests.

TABLE 90-9 Direct Thrombin Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Argatroban	Treatment and prophylaxis of HITT	0.5–1.2 μg/kg/min continuous IV infusion to start titration to goal aPTT between 50 and 85 s Begin VKA therapy; measure INR daily. Stop argatroban when INR > 4. Repeat INR in 4–6 h, if INR is below the desired range and then resume argatroban infusion.	• Signs of bleeding • CBC • aPTT (argatroban and bivalirudin) (not reliable marker with dabigatran) • ACT • PT/INR (false elevation) • Modified thrombin clotting time (dabigatran) • Ecarin clotting time (ECT) (dabigatran) • Renal function (Bivalirudin and argatroban; desirudin and dabigatran) • LFTs (argatroban)	***Precautions*** • Indwelling epidural catheter • Recent major, spinal or ophthalmologic surgery • History of recent major bleed (GI, intracranial, etc.) • Congenital or acquired bleeding disorders • Recent cerebrovascular accident • Hepatic impairment (argatroban) • Renal dysfunction (all agents) ***Contraindications*** • Hypersensitivity to agent or formulation excipients • Severe active bleeding
	Treatment of ACS	LD: 100 μg/kg IV bolus Initial infusion: 1–3 μg/kg/min for 6–72 h; maintain aPTT between 50 and 85 s		
Bivalirudin (Angiomax)	PCI	LD: 0.75 mg/kg IV bolus dose, followed by an infusion of 1.75 mg/kg/h for the duration of the procedure Renal impairment: CrCl < 30 mL/min, 0.75 mg/kg IV bolus dose; then 1 mg/kg/h should be considered. Hemodialysis: 0.75 mg/kg IV bolus dose; then 0.25 mg/kg/h should be considered.		
	Treatment of ACS[a]	LD: 0.1mg/kg IV bolus, followed by 0.25 mg/kg/h. Titration to aPTT 1.5–2 times control		

TABLE 90-9 Direct Thrombin Inhibitors *(continued)*

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
	Treatment and prophylaxis of HITT[a]	0.1 to 0.2 mg/kg/hr, titration to aPTT 1.5–2 times control		
Dabigatran (Pradaxa)	Prophylaxis of VTE in nonvalvular atrial fibrillation	150 mg orally twice daily (Do not open capsule or crush.) Renal impairment: CrCl 15–30 mL/min: 75 mg orally twice daily CrCl 30–50 mL/min and concomitant P-glycoprotein inhibitors: 75 mg orally twice daily		
Desirudin (Iprivask)	Prophylaxis of DVT in postoperative hip replacement	15 mg SC q12 h Renal impairment: CrCl 31–60 mL/min: 5 mg SC q12 h CrCl < 31 mL/min: 1.7 mg SC q12 h		

[a]Indicates off-label use of medication.
HITT, heparin-induced thrombocytopenia with thrombosis; CBC, complete blood count; aPPT, activated partial thromboplastin time; VKA, vitamin K antagonist; ACT, activated clotting time; PT/INR, prothrombin time/ international normalized ratio; INR, international normalized ratio; ACS, acute coronary syndromes; LD, loading dose; LFT, liver function tests; PCI, percutaneous coronary intervention; CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis.

TABLE 90-10 Vitamin K Antagonism: Warfarin

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Warfarin (Coumadin)	Treatment of VTE	Initial dosing: 2.5–10 mg q24 h (see Precautions) titrated to range INR: 2.0–3.0; target of 2.5	• Signs of bleeding • CBC • PT/INR • Genetic testing may be warranted.	***Precautions*** • Lower initial dosing (<5 mg may be warranted in patients who are debilitated, are malnourished, have CHF, have liver disease, have had recent major surgery, or are taking medications known to increase sensitivity to warfarin. • Cerebrovascular disease • Coronary disease • CYP2C9 and VKORC1 genetic variation • Moderate-to-severe hypertension • Malignancy • Renal impairment • Recent trauma • Collagen vascular disease • Conditions that increase risk of hemorrhage, necrosis, and/or gangrene, preexisting • Congestive heart failure • Severe diabetes • Excessive dietary vitamin K • Hepatic impairment • Thyroid disorders
	Atrial fibrillation	Initial dosing: 2.5–10 mg q24 h (see Precautions) titrated to range INR: 2.0–3.0; target of 2.5		
	s/p MI	Initial dosing: 2.5–10 mg q24 h (see Precautions) titrated to range INR: 2.0 – 3.0; target of 2.5		
	Mechanical valve in the aortic position	Initial dosing: 2.5–5 mg q24 h (see Precautions) titrated to range INR 2.0–3.0; target of 2.5		
	Mechanical valve in the mitral position	Initial dosing: 2.5–5 mg q24 h (see Precautions) titrated to range INR 2.5–3.5; target of 3.0		
	Mechanical valve in *both* the aortic and mitral position	Initial dosing: 2.5–5 mg q24 h (see Precautions) titrated to target INR 2.5–3.5; target of 3.0		

TABLE 90-10 Vitamin K Antagonism: Warfarin *(continued)*

Bioprosthetic valve in the mitral position	Initial dosing: 2.5–5 mg q24 h (see Precautions) titrated to target INR 2.0–3.0; target of 2.5 × 3 mo	• Epidural catheters • Infectious diseases or disturbances of intestinal flora, such as sprue or antibiotic therapy • Poor nutritional state • Protein C deficiency • HITT • Vitamin K deficiency ***Contraindications*** • Hypersensitivity to warfarin or any component of the product • Pregnancy, known or suspected • Spinal puncture and other procedures with potential for uncontrollable bleeding • Pericarditis and pericardial effusion • Bleeding tendencies of the gastrointestinal, genitourinary, or respiratory tract • GI, genitourinary or respiratory tract ulcerations or overt bleeding • Cerebrovascular hemorrhage

VTE, venous thromboembolism; CBC, complete blood count; PT/INR, prothrombin time/ international normalized ratio; INR, international normalized ratio; MI, myocardial infarction; HITT, heparin-induced thrombocytopenia with thrombosis.

2. Mechanism of action.
   a. Inhibits the synthesis of all vitamin K–dependent clotting factors (II, VII, IX, X, and protein C and S).

III. FIBRINOLYTICS (Table 90-11)

A. General principles.
   1. Methods of administration.
      a. Intravenous.
      b. Intravascular (i.e., catheter directed).

B. Mechanism of action.
   1. Enhances the conversion of plasminogen to plasmin, initiating degradation of fibrin and subsequent clot lysis.

IV. REVERSAL

A. Antiplatelet agents (Table 90-13).
   1. Interruption of therapy may warrant consultation of specialist in select patient care scenarios (i.e., recent placement of drug-eluting stent).
   2. Administration of desmopressin IV and platelet transfusion may be required.

B. Unfractionated heparin (Table 90-12).
   1. Protamine.
      a. Dose required decreases rapidly as time from heparin administration elapses.
         i. Immediately recent UFH administration: give 1 mg protamine/100 units of heparin administered.
         ii. Thirty to sixty minutes since UFH administration: 0.5 to 0.75 mg protamine for every 100 units of heparin.
      b. Administer slowly with no more than 50 mg in a 10-minute period.
      c. Perform postinfusion aPTT to verify response to reversal.

C. Low molecular weight heparins (Table 90-12).
   1. Protamine.
      a. Provides partial reversal of LMWH products.
      b. Protamine 1 mg neutralizes 100 anti-Xa units *or* 1 mg protamine neutralizes 1 mg of LMWH (e.g., enoxparin) administered.

D. Indirect factor Xa inhibitor fondaparinux (Table 90-13).
   1. Hold agent; duration of effect is dependent upon renal function/clearance.
   2. No pharmacologic reversal agent available; limited data to support reversal strategies may be effective.

E. Direct factor Xa inhibitors (Table 90-13).
   1. Hold agent: duration of effect is dependent upon renal function/clearance and hepatic function.

TABLE 90-11 Fibrinolytics

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions and contraindications
Alteplase (Activase and CathfloActivase)	Acute ST elevation MI	>67 kg LD: 15 mg IV bolus, followed by 50 mg infusion over 30 min, then 35 mg infusion over 60 min (total = 100 mg) ≤67 kg LD: 15 mg IV bolus, followed by 0.75 mg/kg infusion over 30 min (max 50 mg), then 0.5 mg/kg over 60 min (max 35 mg)	• Signs of bleeding • CBC • Blood pressure • ECG • Cranial CT scan, improved neurologic recovery (acute ischemic stroke) • Cardiac enzymes, ECG, resolution of chest pain (acute myocardial infarction) • Fibrinnogen, thrombin time (TT), aPTT, prothrombin time (PT); at baseline, 4 h after therapy initiation, and TT only within 3 h after therapy	***Precautions*** • Recent major or minor surgery (within 10 d) • Cerebrovascular diseases • Recent GI or genitourinary bleeding • Recent trauma • Hypertension: systolic BP ≥ 175–180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects • Severe hepatic or renal dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at a seriously infected site • Advanced age • Patients currently receiving oral anticoagulants • Known or suspected infection in the catheter during use for catheter clearance • Severe neurologic deficit (NIHSS > 22) (ischemic stroke)
	Lysis of massive and submassive PE	Routine administration for PE *(noncardiac arrest)*: 100 mg IV administered over 2 h During cardiopulmonary resuscitation: 50 mg IV single dose administered over 5 min		
	Acute ischemic stroke (within 3 h of symptom onset) Acute ischemic stroke (within 3–4.5 h of symptom onset)	0.9 mg/kg IV (not to exceed 90 mg total dose) infused over 60 min with 10% of the total dose administered as an initial intravenous bolus over 1 min		

(continued)

TABLE 90-11 Fibrinolytics *(continued)*

	Exclusions: Age >80 y: evidence of taking oral anti-coagulant therapy, baseline NIHSS score >25; history of stroke and diabetes		• Patients with major early infarct signs on computerized cranial tomography (ischemic stroke) ***Contraindications*** • Hypersensitivity to agent or formulation excipients • Active internal bleeding • Severe uncontrolled hypertension • Recent intracranial or intraspinal surgery or trauma (within 3 mo) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • History of cerebrovascular accident • Evidence, suspicion, or history of intracranial hemorrhage • Seizure at the onset of stroke (ischemic stroke) • Platelet count < 100,000/mm^3 (ischemic stroke) • Administration of heparin with 48 h preceding the onset of stroke and have an elevated activated partial thromboplastin time at presentation (ischemic stoke)
	Peripheral arterial or venous thrombosis	Catheter-directed administration: 1.5 mg/h by transcatheter intra-arterial infusion until lysis of thrombus	
	Venous catheter occlusion	Weight >30 kg 2 mg/2 mL Patient weight >10 kg but <30kg – 110% of the internal lumen volume, not to exceed 2 mg/2 mL	
Reteplase (Retavase)	Acute ST elevation MI	10 units IV bolus, two doses give 30 min apart	
	Venous catheter occlusion[a]	0.4 units/2 mL	
Tenecteplase (TNKase)	Acute ST elevation MI	<60 kg: 30 mg dose ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg	

[a]Indicates off-label use of medication.
LD, loading dose; CBC, complete blood count; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PE, pulmonary embolism.

TABLE 90-12 Example Protamine Dose Calculation for Unfractionated Heparin and LMWH Reversal[a]

UFH delivery time (hours)	Heparin dose	Patient weight (kg)	Intravenous UFH dose administered (units)	UFH accumulation at 1 h[b,c] (units)	UFH remaining at 2 h[b,c] (units)	UFH remaining at 3 h[b,c] (units)	Protamine dose (mg) required to reverse UFH[d]
0	80 units/kg bolus	80	6,400	3,200	1,600	800	8
0	18 units/kg/h infusion	80	1,440	1,440	720	360	3.6
1	18 units/kg/h infusion	80	1,440	(0)	1,440	720	7.2
2	18 units/kg/h infusion	80	1,440	(0)	(0)	1,440	14.4
Approximate amount of UFH remaining in circulation →						**3,320**	**33.2**

LMWH delivery time (hours)	LMWH dose	Patient weight (kg)	LMWH dose administered (mg)	LMWH remaining within 8 h[b] (mg)	LMWH remaining at 8–12 h[b] (mg)	LMWH remaining after 12 h (mg)	Protamine dose (mg) required to reverse LMWH[d]
0	1 mg/kg q12 h	80	80	80	–	–	80
8	(0)	80	–	–	40	–	40
12	(0)	80	–	–	–	≤20	0–20

[a]Illustration assumes an 80-kg patient given a bolus and infusion for 3 h who developed clinically significant bleeding.
[b]Assumes half-life of heparin to be 1 h.
[c]Calculated amounts of heparin remaining at 1 h following initiation of continuous infusion may be overestimated in this model.
[d]Administer no more than 20 mg of protamine per minute, with a max of 50 mg over any 10-minute period.
Adapted from *Irwin and Rippe's Manual of Intensive Care Medicine*. Lippincott Williams & Wilkins: New York, 2009 (96):587–609.

TABLE 90-13 Reversal Strategies for Select Antithrombotic Agents

Agents	Reversal strategies	Additional considerations
Aspirin	Desmopressin 0.3–0.4 μg/kg IV bolus and/or platelet transfusion	• Interruption of therapy may warrant consultation of specialist in select patient care scenarios (i.e., recent placement of a drug-eluting stent)
$P2Y_{12}$ inhibitors	Platelet transfusion and/or desmopressin 0.3–0.4 μg/kg IV bolus	
Warfarin	INR 4–10 (no signs of bleeding) • Vitamin K; 1–2.5 mg by mouth INR > 10 (no signs of bleeding) • Vitamin K; 2.5–5 mg by mouth • Surgery within 24 h: • Interrupt warfarin • Vitamin K 2.5–5 mg IV Surgery within 48 h: • Interrupt warfarin • Vitamin K 2.5 mg orally Severe or life-threatening bleed: • Interrupt warfarin therapy • Vitamin K 10 mg IV + FFP 15–30 mL/kg • Consider administering three-factor or four-factor (PCC) at 25–50 units/kg (product-specific dosing and maximum dosing) based upon INR value, or rhFVIIa 10–90 μg/kg IV (if no PCC available) as alternative or adjunct therapy	• Close monitoring of INR is needed for patients demonstrating elevations in INR on warfarin therapy and to assess need for supplemental vitamin K • Repeat testing of the INR at 24 h and preoperation may be needed to assess need for supplemental vitamin K or FFP • IV and oral therapy are preferred over SC administration due to erratic absorption • PCC, APCC, and rhFVIIa have been associated with thromboembolic events.

TABLE 90-13 Reversal Strategies for Select Antithrombotic Agents *(continued)*

Agents	Reversal strategies	Additional considerations
Indirect Factor Xa inhibitors[a] (Fondaparinux)	• Interrupt fondaparinux • rhFVIIa 90 μg/kg IV[b,c] • Activated prothrombin complex concentrates • FEIBA 50–100 units/kg IV[b,c]	• Duration of effect is dependent upon renal function/clearance and can range from 13–21 h in healthy persons, and be prolonged in renal dysfunction. • APCC and rhFVIIa have been associated with thromboembolic events. • PCC's and APCC"s are derived from human plasma, thus risk of immune mediated reaction and infection transmission.
Direct Factor Xa inhibitors[a] (Apixaban and Rivaroxaban)	• Interrupt therapy • rhFVIIa 90 μg/kg IV[b,c] • Activated prothrombin complex concentrates • FEIBA 50–100 units/kg IV[b,c]	• Duration of effect is dependent upon renal function/clearance and hepatic function, and can be prolonged in organ dysfunction. • APCC and rhFVIIa have been associated with thromboembolic events.
Direct thrombin inhibitors[a]	• Interrupt therapy • Hemofiltration and hemodialysis may be effective in the removal of bivalirudin, dabigatran, and desirudin • Desmopressin 0.3–0.4 μg/kg IV bolus[b] • Activated prothrombin complex concentrates • FEIBA 50–100 units/kg IV[b,c]	• PCC's are plasma derived and some products may contain heparin.

[a]No specific antidote exists; beneficial effects described in the literature limited to animal models, human laboratory studies, and case reports.
[b]Data based upon animal models, laboratory studies, or case reports.
[c]Reversal data based on laboratory end points, no experience in actively bleeding patients.
INR, international normalized ratio; FFP, fresh frozen plasma; PCC prothrombin complex concentrates; APCC, activated prothrombin complex concentrates; rhFVIIa, recombinant human factor 7a; FEIBA, factor VIII inhibitor-bypassing activity.

2. No pharmacologic reversal agent available; limited data to support reversal strategies may be effective.

F. Direct thrombin inhibitors (Table 90-13).

1. Hold agent; duration of effect is dependent upon renal function/clearance and hepatic function.
2. No pharmacologic reversal agent available; limited data to support reversal strategies may be effective.

G. Warfarin (Table 90-13).

1. Hold warfarin; duration of effect could last up to several days in the absence of reversal agent administration.
2. Treatment with vitamin K (phytonadione), fresh frozen plasma, and/or prothrombin complex concentrate or prothrombin complex concentrate or recombinant factor VIIa.

H. Fibrinolytics.

1. No specific reversal agent is available.
2. Hold agent; duration of effect is agent specific.
3. Elimination half-life varies (alteplase 4 to 8 minutes; tenecteplase 20 to 24 minutes).

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91 Venous Thrombosis and Related Disorders in Critical Care Patients

Mya Sanda Thein, Ashkan Emadi, and Michael B. Streiff

I. VENOUS THROMBOEMBOLISM (VTE)

A. General principles.

1. Includes deep venous thrombosis (DVT), pulmonary embolism (PE), and superficial venous thrombosis (SVT); DVT 65% (90% lower extremity, 10% upper extremity), PE-35%.
2. Epidemiology.
   a. Annual incidence varies by age from 1/100,000 in children to 700/100,000 in 80 year olds.
   b. Annual incidence varies by racial group from 141/100,000 in African Americans to 104/100,000 in Caucasians, 55/100,000 in Latinos, and 21/100,000 in Asians.
   c. Incidence in the intensive care unit (ICU)—2.7% on admission, 9.6% over ICU stay.
3. Etiology: hypercoagulability, stasis, vascular damage (Virchow triad).
   a. Risk factors: see Table 91-1.
   b. ICU-specific risk factors: personal/family history of VTE (hazard ratio [HR] 4.0), end-stage renal disease (HR 3.7), platelet transfusion (HR 3.2), vasopressor use (HR 2.8).
   c. Upper extremity DVT risk factors—central venous catheter (CVC) or pacemaker wires, intrathoracic tumors.

B. Prevention.

1. Assess all patients at admission for risk factors for VTE and contraindications to prophylaxis (see Tables 91-1 and 91-4).
2. VTE prophylaxis: pharmacologic and mechanical (see Tables 91-2 and 91-3); pharmacologic prophylaxis preferred due to greater compliance in routine practice.
3. Dalteparin 5,000 units q24 h superior to unfractionated heparin (UFH) 5,000 units q12 h for prevention of PE in the PROTECT study.
4. Reassess patients' VTE risk factors and contraindications to prophylaxis often.
5. Graduated compression stockings (GCS): size appropriately before application; check daily for skin complications.
6. CVC-VTE prophylaxis: Low-dose warfarin and prophylactic dose anticoagulants (e.g., enoxaparin 40 mg daily) are ineffective. Dose-adjusted warfarin international normalized ratio (INR 1.5 to 2) reduced the incidence of

TABLE 91-1 Inherited and Acquired VTE Risk Factors

Inherited factor	Increase in VTE risk	Acquired factor	Increase in VTE risk
Antithrombin deficiency	15- to 20-fold	Major surgery	10- to 110-fold
Protein C deficiency	15- to 20-fold	Heparin-induced thrombocytopenia	50-fold
Protein S deficiency	5- to 20-fold	Trauma	5- to 50-fold
Factor V Leiden	5-fold	Malignancy	4- to 20-fold
Elevated factor VIII	3- to 6-fold	Age > 70 (vs. age 30)	10-fold
Prothrombin gene 20210 mutation	2- to 3-fold	Immobilization	10-fold
Elevated factor IX antigen	2.5-fold	APS	3- to 10-fold
Elevated factor XI antigen	2.2-fold	Human immunodeficiency virus (HIV) infection	3- to 10-fold
Non-O blood group	1.5- to 1.8-fold	Kidney disease (e.g., nephrotic syndrome, renal transplant)	3- to 10-fold
		Stroke	2- to 9-fold
		Inflammatory disease (e.g., SLE, IBD)	3- to 8-fold
		Central venous catheter	5- to 7-fold
		Oral contraceptives	4- to 7-fold
		Chemotherapy	2- to 6-fold
		Pregnancy/postpartum	3- to 5-fold
		HRT	3- to 5-fold
		Obesity	2- to 3-fold
		Acute infections	1- to 3-fold

CVC-VTE compared to low-dose warfarin in an open randomized clinical trial, but was associated with a trend toward more bleeding complications.

C. Clinical manifestations of VTE.

1. Deep venous thrombosis.
   - **a.** Upper extremity DVT: pain and swelling in arms, neck, face, or chest, dysfunction of CVC.
   - **b.** Lower extremity DVT: cramping pain, swelling, erythema of leg. Groin swelling indicates pelvic vessel involvement; lower abdominal wall swelling, flank collaterals, and bilateral leg swelling indicate inferior vena cava (IVC) involvement.
2. PE—tachycardia, tachypnea, dyspnea, pleuritic chest pain, hypoxemia, hypotension, syncope/presyncope.

TABLE 91-2 VTE Prophylaxis Options

Pharmacologic prophylaxis	Mechanical prophylaxis
Unfractionated heparin	Graduated compression thromboembolus-deterrent (TED) stockings
LMWH • Dalteparin (half-life 4 h) • Enoxaparin (half-life 3.5 h) • Tinzaparin (half-life 4.5 h)	Intermittent pneumatic compression devices (IPCD)
Fondaparinux (half-life 17–21 h)	
Rivaroxaban (half-life 5–9 h)	

TABLE 91-3 Pharmacologic VTE Prophylaxis Regimens

Patient population	Regimen
Medical inpatient and general surgery	Unfractionated heparin 5,000 units q8–12 h Dalteparin 5,000 units q24 h Enoxaparin 40 mg q24 h Fondaparinux 2.5 mg q24 h
Orthopedic surgery (total knee or hip arthroplasty)	Dalteparin 5,000 units q24 h Enoxaparin 30 mg q12 h Enoxaparin 40 mg q24 h Fondaparinux 2.5 mg q24 h Rivaroxaban 10 mg q24 h Warfarin 5 mg q24 h (INR 2–3)
Major trauma	Enoxaparin 30 mg q12 h

Note: Addition of mechanical prophylaxis (IPCD) to pharmacologic prophylaxis has been shown to further reduce VTE in some patients receiving pharmacologic prophylaxis.

TABLE 91-4 Contraindications to VTE Prophylaxis

Pharmacologic prophylaxis	Mechanical prophylaxis
Active or high risk of bleeding	Arterial insufficiency
Indwelling neuroaxial catheter (for enoxaparin 30 mg q12 h, fondaparinux, rivaroxaban, warfarin INR 1.5 or more)	Open wounds
Coagulopathy	Acute DVT
Platelet count < 50,000/μL	

D. Diagnosis of VTE—Wells criteria can be used to assess the likelihood of DVT and PE prior to obtaining diagnostic imaging (see Tables 91-5 and 91-6).

1. Upper extremity DVT.
   - **a.** Duplex ultrasound—imaging study of first choice (97% sensitive, 96% specific); proximal subclavian and brachiocephalic veins difficult to image; duplex ultrasound in stress positions important for diagnosis of thoracic outlet syndrome.
   - **b.** Computed tomographic (CT) venography: if duplex negative and suspicion high, CT venography a worthwhile follow-up study; CT venography valuable in documenting intrathoracic tumors resulting in vascular compression. Corrective surgery is essential for the best long-term outcome with thoracic outlet syndrome.
2. Lower extremity DVT.
   - **a.** Duplex ultrasound—sensitivity 95%, specificity 98%, calf DVT sensitivity 60% to 80%. Sensitivity also lower for iliac vein and IVC.
   - **b.** CT venography recommended if duplex study is negative and iliac, pelvic, or IVC thrombosis is suspected. If an anatomic reason for thrombosis suspected (e.g., May-Thurner syndrome), CT venography essential for establishing the diagnosis.
3. Pulmonary embolism.
   - **a.** CT angiography is study of first choice—sensitivity 94%, specificity 94%.
   - **b.** Ventilation/perfusion ($\dot{V}/\dot{Q}$) scan in patients with intravenous (IV) contrast allergies and renal insufficiency and in pregnant patients.

TABLE 91-5 Wells Clinical DVT Model

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster-cast immobilization of the lower extremities	1
Recently bedridden for 3 d or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than the asymptomatic side (measured 10 cm below the tibial tuberosity	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	–2

Low risk = Wells score <1; Intermediate risk = Wells score = 1 or 2; High risk = 3 or more.

TABLE 91-6 Wells Clinical PE Model

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within 6 mo or currently receiving palliative treatment)	1
Surgery or bedridden for 3 d or more during the past 4 wk	1.5
History of DVT or PE	1.5
Hemoptysis	1
Heart rate >100 beats/min	1.5
PE judged to be the most likely diagnosis	3
Clinical signs and symptoms compatible with DVT	3

Low probability = Score of <2 points; Intermediate probability = 2–6 points; High probability = More than 6 points.

4. D-dimer: not recommend for diagnosis of VTE among inpatients (often elevated in hospitalized patients and suppressed in patients receiving anticoagulants).

E. Treatment.

1. Timing of treatment initiation: If diagnostic suspicion is high for VTE and risk benefit is favorable for anticoagulation then anticoagulation should be initiated immediately. If diagnostic suspicion is intermediate, one could delay initiation of anticoagulation as long as 4 hours to allow diagnostic imaging. If diagnostic suspicion is low, then anticoagulation could be held until diagnostic confirmation is possible up to 24 hours. Wells DVT and PE models are available to assess the likelihood of VTE (Tables 91-5 and 91-6).
2. Acute anticoagulation options (see Table 91-7).
3. Choice of anticoagulant.
   a. Half-life—In patients who may need to have invasive procedures, agents with a shorter half-life may be preferable. Fondaparinux has the longest half-life followed by rivaroxaban, tinzaparin, dalteparin, and enoxaparin, in descending order of half-lives.
   b. Reversibility—In patients likely to have invasive procedures or considered at higher risk of bleeding, use of agents with potential for reversal is advised. UFH is 100% reversible with IV protamine, while tinzaparin (86%), dalteparin (74%), and enoxaparin (54%) are protamine reversible to a lesser degree. No antidotes are available for fondaparinux or rivaroxaban (see also Chapter 90: Antithrombotic Therapy in Critically Ill Patients).
   c. Renal insufficiency—reduced doses of enoxaparin recommended for patients with creatinine clearance (CrCl) < 30 mL/minute; other low molecular weight heparins (LMWHs) may accumulate at reduced CrCl. Do not use fondaparinux and rivaroxaban in patients with CrCl < 30 mL/minute.
   d. Subcutaneous absorption—impaired in patients on vasopressors; subcutaneous absorption can be impaired; IV UFH may be preferable.

TABLE 91-7 Anticoagulation Options for Treatment of Venous Thromboembolism

Anticoagulant	Regimen
LMWH	
• Dalteparin	100 units/kg SC q12 h 200 units/kg SC daily
• Enoxaparin	1 mg/kg SC q12 h 1.5 mg/kg SC daily
• Tinzaparin	175 units/kg SC daily
Oral direct factor Xa inhibitor	
• Rivaroxaban	15 mg q12h for first 3 wk followed by 20 mg once daily
Pentasaccharide	
• Fondaparinux	5 mg (<50 kg) 7.5 mg (50–100 kg) 10 mg (>100 kg)
UFH	80 unit/kg IV bolus followed by 18 units/kg/h IV infusion adjusted to aPTT-based therapeutic range

e. Vitamin K antagonists (warfarin) are generally not initiated during acute management until therapeutic anticoagulation with a parenteral agent is achieved.

f. CVC-associated DVT—CVC removal not necessarily required upon initiation of anticoagulation; if no resolution of symptoms after 1 to 2 weeks of therapy, remove CVC.

4. PE risk stratification—the risk of death from PE varies from <1% to almost 60%. Indicators of submassive PE include demonstration of right ventricular overload on echocardiogram or CT or elevations of troponin or pro–brain natriuretic peptide (BNP). A bedside risk assessment tool, the Pulmonary Embolism Severity Index (PESI) score, can be used to determine a patient's mortality risk (see Table 91-8).

5. Thrombolytic therapy.

a. Indications: massive PE (hypotension systolic blood pressure [SBP] <90 mm Hg); consider for submassive PE if patient judged to be at high risk for adverse outcomes and low risk for bleeding.

b. PE thrombolytic regimen—tissue plasminogen activator (tPA) 100 mg over 2 hours (10 mg bolus followed by 90 mg over 2 hours).

c. Anticoagulation should be discontinued during the thrombolytic therapy infusion and then restarted once the infusion is complete, and the activated partial thromboplastin time (aPTT) is <80 seconds.

d. Catheter-directed pharmacomechanical thrombolytic therapy (CD-PMT) for DVT: consider for patients at low risk for bleeding who have acute extensive proximal (i.e., iliofemoral) DVT; results are best within the first few weeks after thrombosis.

TABLE 91-8 Pulmonary Embolism Severity Index

Predictors	Points assigned
Age, per year	Age, in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse ≥ 110/min	+20
SBP < 100 mm Hg	+30
Respiratory rate ≥ 30/min (assessed with and without oxygen supplementation)	+20
Temperature < 36°C	+20
Altered mental status (defined as confusion, disorientation, or somnolence)	+60
Arterial oxygen saturation < 90%[a]	+20

[a]Arterial oxygen saturation was defined with and without the administration of supplemental oxygen. A total point score for a given patient is obtained by summing the patient's age (in years) and the points for each applicable predictor. Point assignments correspond with the following risk classes: Class I ≤ 65, low risk; Class II 66–85, low risk; Class III 86–105, high risk; Class IV 106–125, high risk; Class V > 125, high risk.

6. IVC filter: IVC filters should be considered in any patient with acute proximal lower extremity DVT and/or PE who cannot be treated with anticoagulation. Patients with isolated *calf* vein DVT who cannot receive anticoagulation can be followed with serial duplex ultrasound (days 3, 7, 14) for progression and reassessed for contraindications for anticoagulation. Use of IVC filters for other indications remains controversial (e.g., PE in patients with cardiopulmonary compromise).
7. Duration of anticoagulation (see Table 91-9)—the duration of anticoagulation for VTE is primarily determined by the presence or absence of precipitating factors at the time of the thrombotic event. Idiopathic VTE (i.e., thrombosis in the absence of identifiable situational triggers) implies the presence of a chronic underlying hypercoagulable state that places the patient at ongoing risk for recurrence in the absence of anticoagulation.
   a. Patients with idiopathic VTE warrant strong consideration of indefinite anticoagulation. Conversely, the presence of a strong situational trigger for thrombosis such as surgery or major trauma warrants short-term therapy (i.e., 3 months) as the risk for thrombosis resolves once the transient thrombophilic state passes. Patients with moderate situational triggers such as hospitalization for an infection are at intermediate risk for recurrent thrombosis.
   b. A meta-analysis of observational studies of VTE found that the annual risk of recurrent thrombosis after completion of a course of therapy for a VTE associated with a surgical trigger, a nonsurgical trigger, and idiopathic events was 0.7% per year, 4.2% per year,

TABLE 91-9 Duration of Therapy for Venous Thromboembolism

Venous thromboembolism	Duration of therapy
Triggered DVT (e.g., associated with surgery, trauma)	3 mo
Triggered PE (e.g., associated with surgery, trauma)	3 mo
Idiopathic DVT	At least 3 mo, consider indefinite
Idiopathic PE	At least 3 mo, consider indefinite
Cancer-associated VTE	Indefinite or as long as cancer active or under therapy
Recurrent VTE	Indefinite therapy
VTE associated with high-risk thrombophilia (e.g., antithrombin, protein C, protein S deficiency, APS, homozygous factor V Leiden or prothrombin gene mutation, compound heterozygosity for factor V Leiden and the prothrombin gene mutation)	Indefinite therapy
VTE associated with moderate-risk or low-risk thrombophilia (e.g., factor V Leiden heterozygosity, prothrombin gene mutation heterozygosity)	Dictated by presence or absence of situational triggers
Distal DVT (e.g., calf)	3 mo

and 7.4% per year, respectively. Because only 50% of patients with idiopathic VTE suffer recurrent VTE within 10 years of discontinuing anticoagulation, risk stratification models such as the Vienna criteria (for Web-based calculator, go to http://www.meduniwien.ac.at/user/georg.heinze/zipfile/ViennaPredictionModel.html) can help to assess a patient's risk for recurrence. Since recurrent events typically mirror initial events 75% of the time (DVTs recur as DVTs, PEs as PEs), it is generally worthwhile considering longer-term therapy more seriously for patients with PE. The risk for bleeding complications can be estimated using prediction rules such as the HASBLED score (for a Web-based calculator, go to http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/).

8. Recurrent VTE despite anticoagulation (see Table 91-10)—The components of Virchow triad that are important for initial VTE are equally valid for recurrent thrombosis. Hypercoagulability due to subtherapeutic anticoagulation or thrombophilic disorders such as heparin-induced thrombocytopenia, Trousseau syndrome, or antiphospholipid syndrome (APS) must be considered. It is equally important to consider conditions

TABLE 91-10 Recurrent VTE: Management Strategies

Clinical scenario	Management
Subtherapeutic anticoagulation	• Resume parenteral anticoagulation until therapeutic INR achieved with vitamin K antagonist • Consider higher INR target range (2.5–3.5) • Consider chronic parenteral anticoagulation (e.g., LMWH, fondaparinux) • Consider rivaroxaban
Recurrent upper extremity thrombosis	• If associated with CVC, remove catheter and continue anticoagulation • Consider anatomic vascular compression (e.g., thoracic outlet syndrome, Paget-Von Schroetter–effort thrombosis, thoracic tumor/adenopathy) and treat underlying cause plus anticoagulation ± surgery or pharmacomechanical thrombectomy/thrombolysis
Recurrent lower extremity thrombosis	• If associated with CVC, remove catheter and continue anticoagulation • Consider anatomic vascular compression (e.g., May-Thurner syndrome–iliac vein compression, pelvic tumor/adenopathy) and treat underlying cause plus anticoagulation ± pharmacomechanical thrombectomy/thrombolysis
Heparin-induced thrombocytopenia/ thrombosis	Evaluate for HIT/T (see Chapter X)
Trousseau syndrome	Discontinue vitamin K antagonist and initiate long-term parenteral anticoagulation with UFH/ LMWH/fondaparinux
APS	Evaluate for APS; institute parenteral anticoagulation until therapeutic vitamin K antagonist therapy achieved; consider higher INR target range (INR 3–4 vs. INR 2–3 if therapeutic at the time of VTE)

that might induce stasis/impaired blood flow and/or vascular wall damage such as CVC, thoracic outlet syndrome, May-Thurner syndrome, or tumor-associated vascular compression. Management recommendation for each of these scenarios is displayed in Table 91-9.

II. THROMBOHEMORRHAGIC EVENTS IN MYELOPROLIFERATIVE NEOPLASMS

A. General principles.

1. Philadelphia chromosome–negative chronic myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

   a. PV—annual incidence: 2 per 100,000 population with median age of 70 years; at initial presentation, the incidence of thrombosis and bleeding is 12% to 39% and 2% to 20%, respectively.
   b. ET—annual incidence: 0.5 to 2.5 per 100,000 population with median age of 60 years; the overall risk of thrombosis and bleeding in ET has been reported 6.6% per patient-year and 0.33% per patient-year, respectively.
2. *JAK2*-V617F.
   a. Somatic gain-of-function mutation that involves the *JAK2* tyrosine kinase gene, typically in exon 14 mutation (*JAK2*V617F).
   b. The presence of *JAK2*V617F is associated with an increased risk of arterial and venous thrombosis, particularly in ET.

B. Clinical features.

1. Thrombosis in PV and ET occurs in arterial, venous, or microcirculation.
2. Large-vessel arterial events: predominant cause of morbidity and mortality including cerebrovascular accidents (stroke and transient ischemic attacks [TIA]), myocardial infarction (MI), and peripheral arterial occlusion.
3. Lower extremity DVT and PE account for the majority of venous events.
4. Associated with a high rate of intra-abdominal (portal and hepatic) vein thromboses that account for a substantial proportion of potentially catastrophic events, particularly in younger women with PV. Underlying MPN was reported in 31% and 53% of patients presenting with otherwise unexplained (i.e., without cirrhosis or hepatobiliary carcinoma) portal or hepatic vein thrombosis, respectively, in one study.
5. Associated with microcirculatory symptoms (headache, paraesthesias, erythromelalgia), which are more common in ET than PV, such as erythromelalgia.
6. Pathogenesis of thrombohemorrhagic events in PV and ET thought to be related to erythrocytosis, thrombocytosis, functional and structural platelet abnormalities, platelet membrane receptor abnormalities, leukocyte activation, and acquired von Willebrand syndrome.

C. Bleeding in ET and PV.

1. Involves primarily the skin and mucous membranes (suggests defective primary hemostasis) including ecchymosis, epistaxis, menorrhagia, and gingival hemorrhage; gastrointestinal bleeding is less frequent.
2. Often associated with aspirin use.
3. Can be severe, requiring hospitalization and blood transfusion.

D. Surgical procedures.

1. Associated with an even higher morbidity and mortality in patients with MPN due to both thrombosis and hemorrhage.
2. Risks particularly high when underlying disease is poorly controlled (erythrocytosis in PV or thrombocytosis in both PV and ET).

E. Diagnosis.

1. PV and ET: diagnostic criteria (see Table 91-11).
2. MPN-related thrombosis.

TABLE 91-11 Requirements for Diagnosis and Treatment of Polycythemia Vera and Essential Thrombocythemia

Polycythemia vera	Essential thrombocythemia
Elevated red cell mass and normal or elevated plasma volume	Persistent thrombocytosis > 400 × 10^9/L in the absence of a reactive cause
Normal arterial O_2 saturation	Absence of iron deficiency (normal serum ferritin for gender)
Splenomegaly	Hemoglobin < 16 g/dL in a man or < 14 g/dL in woman in the absence of splenomegaly
If no splenomegaly, any two of the following: • Leukocytosis > 12 × 10^9/L • Thrombocytosis > 400 × 10^9/L • Leukocyte alkaline phosphatase > 100 • Serum B_{12} > 900 pg/mL • Unbound B_{12}–binding capacity > 2,200 pg/mL	Red cell mass and plasma volume normal (determinations are mandatory if a *JAK2* V617F assay is positive) Negative Bcr-Abl Fluorescent *in situ* hybridization (FISH) (peripheral blood) if a *JAK2* V617F assay is negative If there is anemia or macrocytosis or leukopenia, or evidence of extramedullary hematopoiesis (i.e., circulating nucleated erythrocytes, immature myelocytes,or splenomegaly), a bone marrow examination (including flow cytometry and cytogenetics) is mandatory regardless of *JAK2* V617F expression status

a. Brain magnetic resonance angiography (MRA) or magnetic resonance venography (MRV), CT angiography, duplex ultrasound, and coronary angiography, depending on suspected location of thrombosis.

b. Any persistent abdominal pain requires contrast CT scan of hepatic, portal, and mesenteric veins.

F. Treatment.

1. Acute venous thrombosis.

a. Initial management is heparin or LMWH followed by oral anticoagulant therapy.

b. Systemic anticoagulation alone may not be sufficient to prevent recurrent thrombosis; treatment of MPN usually also is required (see sections 3–7 below).

2. Acute arterial events.

a. Initial treatment is the same as for events unassociated with MPN.

b. Treatment of MPN usually also is required (see sections 3–7 below).

3. Treatment of MPN.

a. Does not cure the underlying disease or prevent clonal evolution to acute leukemia in either PV or ET. For patients who have experienced thrombosis, goal is prevention of a recurrent thrombotic event.

4. Treatment of PV.
   a. Cytoreductive therapy (e.g., hydroxyurea) usually administered to patients who have experienced thrombosis.
   b. Phlebotomy usually used if no prior thrombosis; hematocrit target <45% associated with significantly lower rates of cardiovascular death and major thrombosis than hematocrit target of 45% to 50%.
5. Treatment of ET.
   a. Cytoreductive therapy (e.g., hydroxyurea) usually administered to patients who have experienced thrombosis. Goal of therapy is to keep platelet count $<400 \times 10^9$/L.
6. Low-dose aspirin (100 mg/day).
   a. PV: low-dose aspirin (100 mg/day) reduces both arterial and venous thrombosis.
   b. ET patients with platelet count >1,000,000/μL: hemorrhagic effects of antiplatelet therapy and acquired von Willebrand disease, if present, may be additive.
7. Ruxolotinib: A food and drug administration (FDA)-approved JAK1/2 inhibitor for treatment of patients with PMF; ongoing clinical trials for evaluation of safety and efficacy in PV and ET.

G. Prognosis: Compared with the general population. Ten-year relative survival ratios 0.64, 0.68, and 0.21 in patients with PV, ET, and PMF, respectively.

III. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

A. General principles.

1. Definition: A rare clonal hematopoietic stem cell disorder that causes episodic intravascular hemolytic anemia, abdominal pain, esophageal spasm, fatigue, thrombosis, and bone marrow suppression.
2. May be isolated or occur in the setting of bone marrow failure (aplastic anemia or hypocellular myelodysplastic syndromes [MDS]).
3. Thrombosis occurs in about 40% of paroxysmal nocturnal hemoglobinuria (PNH) patients; venous thrombosis is more common than arterial thrombosis.
   a. Large PNH clones (>50% of granulocytes affected) and classical symptoms (hemolytic anemia and hemoglobinuria) have a greater propensity for thrombosis.
4. Molecular characteristics: Mutations in the X-linked *PIG-A* (phosphatidylinositol glycan class A) gene present in the PNH stem cell and all of its progeny, which is critical for expression of cell surface glycosylphosphatidylinositol-anchored proteins (GPI-AP), lead to lack of membrane inhibitor of reactive lysis (CD59) and decay-accelerating factor (CD55) on membranes of circulating blood cells.
5. Pathogenesis of thrombosis in PNH is complex, including intravascular hemolysis, increased platelet aggregation and adhesion, and accelerated fibrin clot formation due to nitric oxide depletion, increased thrombin generation resulting from platelet microvesicle formation and changes in

the platelet membrane due to complement-mediated damage, perturbed fibrinolysis due to the loss of GPI-anchored urokinase receptor, and decreased activity of tissue factor pathway inhibitor (TFPI).

B. Clinical presentation.

1. Thrombosis: venous and/or arterial at unusual locations (e.g., hepatic vein thrombosis/Budd-Chiari syndrome, sagittal vein thrombosis).
2. Severe abdominal pain crises, severe headaches, back pain, excessive weakness, fatigue, and recurrent infections.
3. Hemoglobinuria occurs in 50% or less of patients. Frequently, patients notice their urine is a dark tea color.

C. Diagnosis.

1. Flow cytometry: identifies blood cells (typically erythrocytes and leukocytes) that lack GPI-AP.
   a. Flow cytometry using fluorescein-labeled proaerolysin variant (FLAER)—a bacterial protein that binds to GPI anchors (more sensitive than CD59 flow cytometry).
   b. PNH clone size best determined by assessment of granulocytes and monocytes, as recent hemolytic episodes/blood transfusion can affect the proportion of erythrocytes that express GPI-AP.

D. Treatment.

1. Allogeneic hematopoietic stem cell transplantation.
   a. The only curative therapy for PNH; best candidates are younger patients with severe pancytopenia or life-threatening thrombosis who have a human leucocyte antigen (HLA)-identical sibling.
2. Eculizumab.
   a. First effective drug therapy for PNH (approved by the FDA in 2007)
   b. Humanized monoclonal antibody against C5 that inhibits terminal complement activation.
   c. Leads to significant reduction in hemolysis and increased transfusion independence, lessened fatigue, mitigation of the smooth muscle dystonias, and improved overall health-related quality of life.
   d. Leads to 85% absolute reduction in the risk for thrombosis while on eculizumab treatment (thromboembolism rate 1.07 events/100 patient-years compared to 7.37 events/100 patient-years post- and pre-eculizumab, respectively, in one study).
   e. May be associated with an increased risk for *Neisseria* infections due to pharmacologic blockade of the terminal complement complex; must vaccinate all patients treated with eculizumab against *Neisseria meningitidis* before administering drug.
3. Anticoagulation.
   a. Appropriate for initial phase of treatment in individuals with PNH who experience thrombosis.
   b. Chronic anticoagulation: significantly reduces the thrombotic event rate in patients with large PNH clone size, associated with an overall risk of 7.6 bleeding complications per 100 patient-years with the

risk increasing to 11.0 bleeding complications per 100 patient-years during the first 90 days of treatment.

c. Whether anticoagulants can be reduced or eliminated in patients with PNH receiving eculizumab is the subject of future investigation.

E. Prognosis.

1. Thrombosis is an ominous complication of PNH and the leading cause of death.

IV. CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

A. General principles of APS.

1. Autoimmune disorder characterized by both production of antibodies directed against phospholipid-binding proteins (APL) and arterial and/or VTE or recurrent miscarriages (see Table 91-12).

B. General principles of catastrophic antiphospholipid syndrome (CAPS).

1. Rare, life-threatening manifestation of APS.
2. Occurs in <1% of APS patients.
3. Characterized by acute onset, multiorgan failure (kidneys, brain, liver, etc.)
4. Almost always requires ICU-level care.

C. Pathophysiology of CAPS.

1. Often triggered by infections, major surgery, or discontinuation of immunosuppression or anticoagulation.
2. Diffuse microvascular thrombosis leads to tissue ischemia and organ failure (see Table 91-13).
3. Potential mechanisms involve endothelial damage or activation by APL or APL-induced monocyte adhesion to endothelial cells, platelet activation by APL binding to platelet membrane phospholipid-bound annexins, increased monocyte and endothelial cell tissue factor (TF) activity, production of proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), and activation of complement.

D. Diagnosis of CAPS.

1. Based on International Classification Criteria for CAPS (see Table 91-14).
2. Differential diagnosis includes severe sepsis, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), infectious purpura fulminans (IPF), and heparin-induced thrombocytopenia thrombosis (HIT/T).

E. Treatment of CAPS.

1. General: treatment of potential precipitating factors.
2. Broad-spectrum antibiotics for infections.
3. Aggressive hemodynamic resuscitation in case of shock.
4. Debridement or amputation for necrotic tissues.
5. Mechanical ventilation.
6. Renal replacement therapy.
7. Stomach acid suppression.

TABLE 91-12 Diagnostic Criteria for Antiphospholipid Syndrome

Criteria	Definitions
Clinical criteria	
Vascular events	One or more objectively confirmed symptomatic episodes of arterial, venous, or small vessel thrombosis. Histopathologic specimens must demonstrate thrombosis in the absence of vessel wall inflammation to qualify
Pregnancy morbidity	One or more unexplained fetal deaths at or beyond the 10th wk of pregnancy with normal fetal morphology, or One or more premature births of a morphologically normal neonate before the 34th wk of pregnancy due to eclampsia or severe preeclampsia or placental insufficiency, or Three or more unexplained consecutive spontaneous abortions before the 10th wk of gestation in the absence of maternal anatomic, chromosomal, or hormonal abnormalities or paternal chromosomal abnormalities
Laboratory criteria	
Lupus anticoagulant	Positive test for a lupus anticoagulant using a phospholipid-dependent clotting assay (aPTT, dilute Russell Viper venom assay, Kaolin clotting time, dilute prothrombin time [PT]) with evidence of phospholipid dependence present on two or more occasions at least 12 wk apart
Anti–cardiolipin antibody	IgG or IgM anti–cardiolipin antibody measured using a standardized enzyme-linked immuno sorbent assay (ELISA) that is present in medium or high titer (i.e., >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 wk apart
Beta-2 glycoprotein 1 antibody	Anti–beta-2 glycoprotein-I IgG or IgM antibody measured using a standardized ELISA that is present in high titer (>the 99th percentile), on two or more occasions at least 12 wk apart

8. Control of malignant hypertension in case of renal artery or vein thrombosis.
9. Intravascular instrumentation, especially arterial, should be minimized because of the potential to trigger new clots.
10. Anticoagulation (first-line therapy).
    a. UFH infusion.
        i. Sixty to eighty units/kg bolus, followed by 15 to 18 units/kg/h to achieve therapeutic aPTT.
        ii. If the patient previously had been anticoagulated with warfarin prior to detection of CAPS, it usually is held while therapeutic-dose heparin is administered. Upon discharge from ICU, warfarin can

TABLE 91-13 Clinical Manifestations of the Catastrophic Antiphospholipid Antibody Syndrome

Anatomic site	Possible manifestation
Lung	Acute respiratory distress syndrome (ARDS): most common
	Pulmonary hypertension with normal cardiac output and pulmonary capillary wedge pressure
	Pulmonary hemorrhage
Kidney	50% increase in serum creatinine
	Severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 h)
Brain	Stroke
	Encephalopathy
	Seizure
	TIA
Heart	Valvular lesions: Libman-Sacks endocarditis
	MI
	Heart failure
Skin	Livedo reticularis
	Skin ulcers
	Digital ischemia
	Purpura
	Skin necrosis
Peripheral vasculature	DVT/PE
	Arterial thrombosis: most common = femoral artery
	Portal vein and IVC thrombosis
	Retinal artery and vein thrombosis
Blood	Coombs positive hemolytic anemia
	Thrombocytopenia
	DIC
	Bone marrow infarct

be (re-)started; therapeutic anticoagulation with heparin should be continued until INR is in desired range.

11. Corticosteroids (first-line therapy).
    a. Mechanism of action: decreases nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and decreases expression of inflammatory mediators.
    b. Pulse methylprednisolone (1,000 mg/day) IV for 3 to 5 days followed 1 to 2 mg/kg/d.
12. Intravenous immunoglobulins (IVIG) (second-line therapy).
    a. Frequently necessary in the absence of a clinical response or ongoing thrombosis despite first-line treatment.
    b. Several potential mechanisms of action, including interference with APL activity.
    c. Total dose = 2 g/kg (400 mg/kg for 5 days or 1,000 mg/kg for 2 days).

TABLE 91-14 Diagnostic Criteria for the Catastrophic Antiphospholipid Antibody Syndrome

Criteria

1. Evidence of involvement of three or more organ systems, and/or tissues
2. Development of manifestations simultaneously or in <1 wk
3. Confirmation by histopathology of small vessel occlusion in at least one organ/tissue
4. Laboratory confirmation of the presence of APL (i.e., IgG/IgM anti–cardiolipin antibodies >40 GPL or MPL units or anti–beta-2-glycoprotein I antibodies >99th percentile or positive lupus inhibitor on coagulation testing)

Interpretation

Definite CAPS	All four criteria
Probable CAPS	All four criteria, except for involvement of only two organs, systems, and/or tissues *or*
	All four criteria, except for the absence of laboratory confirmation at least 12 wk apart attributable to the early death of a patient never tested for APL before the catastrophic APS *or*
	1, 2, and 4 *or*
	1, 3, and 4 and the development of a third event in more than 1 wk but <1 mo, despite anticoagulation treatment

d. In case of renal insufficiency, use non–sucrose-containing products.
e. Contraindicated unless one can administer immunoglobulin A (IgA)-free product in patients with IgA deficiency (rare) due to risk of anaphylaxis (confirm that IgA is present before dosing).

13. Plasmapheresis (second-line therapy).
a. Remove pathogenic antibodies and cytokines.
b. Exchange 2 to 3 L of plasma for a minimum of 3 to 5 days.
c. β2-GPI levels can be used as a marker of response to plasma exchange.
d. Unclear which treatment (plasma exchange or IVIG) is superior. Concurrent or sequential therapy with IVIG is unclear to be beneficial.

14. Fibrinolytics (third-line treatments): Indicated in life- or limb-threatening venous or arterial thrombosis after risk–benefit calculation.
15. Cyclophosphamide: multiple protocols exist.
16. Prostacyclin: 5 ng/kg/min for 7 days (per case reports).
17. Rituximab: 375 mg/m^2 weekly for 4 weeks.

F. Prognosis of CAPS.

1. Mortality rate remains as high as 48% despite all therapies.
2. Clinical manifestations associated with a poor prognosis and higher mortality include the following:
a. Renal involvement.
b. Splenic involvement.

c. Pulmonary involvement.
d. Adrenal involvement.
e. Systemic lupus erythematosus (SLE) diagnosis.

3. Recurrent CAPS is unusual; patients usually have a stable course with continued anticoagulation.
4. One-fourth of the survivors will develop further APS-related events, but it is rare to develop recurrent CAPS.

V. DRUG-ASSOCIATED THROMBOSIS

A. Oral and transdermal contraceptives.

1. VTE risk increases within 3 to 4 months of the initiation and decreases to previous levels within 3 to 4 months of cessation.
2. Combined second-generation oral contraceptives (contain levonorgestrel or norgestrel): two- to fourfold increased risk.
3. Third-generation oral contraceptives (contain desogestrel or gestodene): 3.5-fold to 7-fold increased VTE risk.
4. Fourth-generation oral contraceptives (contain drospirenone): four- to sixfold increased VTE risk.
5. Transdermal contraceptives: estimated twofold increased VTE risk.
6. Progestin-only contraceptives: lower risk of VTE than estrogen-containing contraceptives.
7. Risk further increased by the presence of thrombophilic conditions, obesity, age >35 years, and smoking.

B. Hormone replacement therapy (HRT).

1. Two- to threefold increase in VTE risk.
2. VTE risk is greatest in the first year of treatment.
3. VTE risk is higher in older, obese women with hereditary thrombophilia or a past history of VTE.
4. VTE risk is lower with transdermal HRT compared with oral HRT.

C. Chemotherapy.

1. Increases VTE risk 6.5-fold.
2. Risk factors (see Khorana VTE Risk Score Table 91-15).
3. Efficacy of prophylactic anticoagulation remains to be demonstrated.

D. Tamoxifen and raloxifene.

1. Frequency of VTE varies with the patient population exposed to tamoxifen.
   a. Premenopausal women with breast cancer: chemotherapy and tamoxifen (3% VTE frequency) versus chemotherapy alone (1%).
   b. Postmenopausal women with breast cancer: tamoxifen and chemotherapy (8%) versus tamoxifen alone (2.3%) versus untreated patients (0.4%).

E. Thalidomide and lenalidomide.

1. Risk of thrombosis with these agents alone (1% to 3%) increases when combined with dexamethasone and/or anthracyclines (10% to 20%).
2. Thromboprophylaxis.
   a. LMWH probably more effective than aspirin.

TABLE 91-15 Khorana VTE Risk Model for Ambulatory Cancer Patients Receiving Chemotherapy

Characteristic	Risk score
Site of primary cancer	
Very high risk (pancreas, stomach)	2
High risk (lung, lymphoma, gynecology, bladder, testicular)	1
Platelet count ≥ 350,000/μL (prechemotherapy)	1
Hemoglobin < 10 g/dL or use of erythropoietic stimulatory agents	1
Leukocyte count > 11,000/μL (prechemotherapy)	1
BMI ≥ 35 kg/m^2	1

Low VTE risk (0.3%–0.8% during first 2.5 mo of chemotherapy) = 0 points; Intermediate VTE risk (1.8%–2% during first 2.5 mo of chemotherapy) = 1 or 2 points; High VTE risk (6.7%–7.1% during first 2.5 mo of chemotherapy) = 3 or more points.

b. LMWH (enoxaparin 40 mg once daily or dalteparin 5,000 units once daily) or full-dose warfarin: appropriate for patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy, unless a contraindication.

3. Aspirin recommended only for low VTE risk patients at high risk for bleeding.

F. Erythropoietin.

1. Must not be administered with hemoglobin >10 g/dL due to increased mortality, as observed in chronic kidney disease patients given erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels ≥11 g/dL.

2. Also has been associated with a 1.5-fold increased risk of VTE in cancer patients.

3. Package insert: "Erythropoiesis-stimulating agents (ESAs) increased the risk of serious cardiovascular events, thromboembolic events, stroke, and mortality in clinical studies when administered to target hemoglobin levels >11 g/dL (and provide no additional benefit); a rapid rise in hemoglobin (>1 g/dL over 2 weeks) may also contribute to these risks… [t]o decrease…risk of cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions."

G. Antipsychotics.

1. Atypical antipsychotics (clozapine, quetiapine, olanzapine, risperidone) associated with a twofold increased risk of VTE.

2. Low-potency antipsychotics (e.g., chlorpromazine) associated with a higher risk than high-potency antipsychotics (e.g., haloperidol).

3. Further increase in VTE risk in the initial 3 months of treatment with use of >1 antipsychotic and with supratherapeutic serum drug concentrations.

4. Mechanism may involve drug-induced sedation, obesity, hyperleptinemia, antiphospholipid antibodies, or activation of platelets or coagulation proteins.
5. Weigh risks and benefits carefully in patients who have suffered VTE.

H. Thrombopoietin receptor agonists—Eltrombopag and Romiplostim.

1. Therapeutic goal: platelet count ≥ 50 × 10^9/L.
2. Thrombosis risk may be higher with platelet count > 200 × 10^9/L.
3. Need to reduce dose of Romiplostim by 1 mcg/kg, and reduce daily dose of Eltrombopag by 25 mg if platelet count > 200 × 10^9/L.
4. Withhold dose and follow platelet count weekly if platelet count > 400 × 10^9/L.

VI. MAJOR TRAUMA-ASSOCIATED THROMBOSIS

A. General principles.

1. Very-high risk for VTE in patients with major trauma with an injury severity score (ISS) ≥9 in the absence of prophylaxis (venographic DVT 58%).
2. Patients receiving enoxaparin prophylaxis have an incidence of DVT as high as 31%.
3. Risk factors for VTE in the major trauma patient (see Table 91-16).

B. Mechanism.

1. Virchow triad.
   a. Stasis (accumulation of activated coagulation factors, damage to endothelial cells due to decreased oxygen and nutrient delivery).
   b. Vessel wall damage/dysfunction (exposes subendothelial TF, collagen leading to activation of platelets and coagulation).
   c. Hypercoagulability (increased coagulation factor levels, increased TNF, increased leukocyte production).
2. Shock/serious injury diminishes anti–thrombin-III (AT-III) levels in the trauma and ICU patients.
3. Elevated plasminogen activator inhibitor 1 (PAI-1) levels, which inhibit tPA and decrease the production of plasmin, suppress fibrinolysis.

TABLE 91-16 Risk Factors for VTE in Patients with Major Trauma

Pelvic and or lower extremity fractures
Spinal cord injury
Injuries requiring surgical intervention
Femoral venous catheters
Major venous injuries
Age > 40
Prolonged immobility
Delayed institution of thromboprophylaxis

C. Diagnosis: depends on the anatomic site.

1. Lower or upper extremities: duplex ultrasound.
2. Lung (pulmonary emboli): helical CT or $\dot{V}/\dot{Q}$ scan.
3. Brain: MRV or computed tomography venogram (CTV).
4. Venogram is useful in all locations but rarely available and not infallible.

D. Prophylaxis.

1. Moderate-risk trauma patients (i.e., no major VTE risk factors) without contraindications: *enoxaparin 30 mg subcutaneously q12 hours*; significantly more effective than 5,000 units UFH subcutaneously twice daily with an estimated decrease in risk of DVT from baseline, 47%, compared with UFH (only 30% decrease).
2. High-risk trauma patients: enoxaparin at above dose plus mechanical prophylaxis (sequential compression devices and GCS).
3. Patients with contraindications to pharmacologic VTE prophylaxis (intracranial bleeding, active bleeding, spinal hematoma): mechanical prophylaxis until contraindication is no longer present.
4. Vena cava filters or surveillance duplex ultrasonography: insufficient data to recommend use.

E. Initial treatment.

1. UFH or LMWH in therapeutic doses. Rivaroxaban less attractive if the patient at high risk for bleeding given that there is no antidote currently available.
2. If high risk of bleeding, UFH without bolus is preferable to LMWH or rivaroxaban.
3. If contraindication to anticoagulation, strongly consider a vena cava filter for proximal DVT or PE.
4. Give UFH/LMWH for at least 5 to 7 days; continue until an INR of 2 or more is achieved with warfarin.
5. Thrombolysis: reserve for trauma patients without contraindications *and* life- or limb-threatening thrombosis.

F. Long-term treatment.

1. Usually warfarin is used. Rivaroxaban is also a possibility if low risk for bleeding, adequate renal and hepatic function.
2. Duration of therapy: 3 months (DVT) to 6 months (PE).
3. Vena cava filters.
   a. Transient contraindication to anticoagulation: consider retrievable vena cava filter.
   b. Long-term contraindications to anticoagulation: consider permanent vena cava filter.

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92 Anemia in the Critical Care Patient

Thomas G. DeLoughery

I. EPIDEMIOLOGY OF ANEMIA IN CRITICALLY ILL PATIENTS

A. Ninety-five percent of patients admitted to intensive care settings become anemic.

B. Half of the patients in the intensive care unit (ICU) will receive red cell transfusion.

C. Most common etiologies.

1. Inflammation (i.e., anemia of chronic disease).
2. Blood loss.
3. Hemolysis.

II. CLASSIFICATION OF ANEMIA

A. Indices—classifies anemia by size of red cells (measured in femtoliters, fL).

1. Microcytic (<80 fL)—caused by interfering with hemoglobin production.
a. Iron deficiency.
b. Anemia of chronic disease.
i. Thirty percent of cases are microcytic.
ii. Etiology: inhibition of iron delivery to developing red cells.
c. Thalassemia.
d. Sideroblastic anemia.

2. Macrocytic anemia.
a. Two forms:
i. Round macrocytes—excess red blood cell (RBC) membrane.
(a) Liver disease.
(b) Alcohol abuse.
(c) Renal disease.
ii. Oval macrocytes due to interference with DNA synthesis.
(a) Megaloblastic anemia (e.g., B_{12} and folate deficiency).
(b) Myelodysplastic syndrome.
(c) Chemotherapeutic agents.

B. Mechanism.

1. Blood loss.
2. Hemolysis.
3. Production defects.
a. Nutritional deficiencies.
b. Anemia of chronic disease.

c. Erythropoietin deficiency (e.g., in renal insufficiency).
d. Aplastic anemia/pure red cell aplasia.
e. Myelodysplastic syndromes.
f. Thalassemias.

III. ANEMIA DUE TO BLOOD LOSS

A. Overt blood loss (e.g., trauma, gastrointestinal bleeding).
B. Subtle blood loss (e.g., through routine phlebotomy for laboratory testing).
1. Average ICU daily blood loss may approximate up to 240 mL/day in some patients.
2. Minimize laboratory draws and "batch" laboratory testing.

IV. HEMOLYTIC ANEMIA: BASIC PRINCIPLES

A. Many processes lead to destruction of red cells (see individual disorders, in subsequent text).
B. Laboratory diagnosis—can be difficult to assess hemolysis if it is subtle or patient has other abnormalities.
1. Indirect bilirubin—sensitive but not specific.
a. Elevated in liver disease and Gilbert syndrome.
2. Lactate dehydrogenase (LDH)—sensitive but not specific.
a. Elevated in liver disease, myocardial infarctions, and rhabdomyolysis.
3. Haptoglobin—specific but not sensitive.
a. Acute-phase reactant.
b. In 2% of the population haptoglobin is genetically absent.
4. Coombs test (i.e., direct antiglobulin test)—sensitive but not specific for autoimmune hemolytic anemia.
a. False positives are seen in renal disease, human immunodeficiency virus (HIV), and liver disease, and in patients who have received intravenous (IV) immunoglobulin.

V. ACQUIRED HEMOLYTIC ANEMIAS

A. Autoimmune.
1. Warm antibody.
a. Clinical presentation: acute onset of severe anemia; patient can complain of back pain and dark urine.
b. Risk factors: lupus, chronic lymphocytic leukemia, or idiopathic
c. Diagnostic testing.
i. Coombs test: immunoglobulin G (IgG) positive ± C3d positive.
d. Therapy.
i. Corticosteroids—prednisone 1 mg/kg daily.
ii. Transfusions: can be difficult to cross-match; choose "least incompatible" units.
iii. Refractory cases—rituximab or splenectomy.

2. Cold agglutinin disease.
   a. Clinical presentation: anemia of variable severity, often worse in cold weather; acrocyanosis often present.
   b. Risk factors.
      i. Acute—sequelae of viral illness (e.g., mycoplasma).
      ii. Chronic—lymphoproliferative disease.
   c. Diagnostic testing.
      i. Coombs test: C3d positive, IgG negative.
   d. Therapy.
      i. Corticosteroids, splenectomy typically ineffective.
      ii. Rituximab may be effective.
      iii. Plasma exchange for cases of severe anemia.
      iv. Avoidance of cold if anemia mild or moderate and compensated.
      v. If transfusion required need to warm blood.
3. Drug induced.
   a. Clinical presentation: acute onset of anemia in the setting of exposure to one or more offending drugs.
   b. Risk factors: exposure to offending drugs (Table 92-1).
   c. Diagnostic testing.
      i. Coombs test: positive (usually IgG).
   d. Therapy.
      i. Stop offending agent.
      ii. RBC transfusions.
      iii. Immunosuppression with corticosteroids rarely is required.

B. Microangiopathic (also see Thrombocytopenia, Chapter 89).

1. Clinical presentation—hemolytic anemia of variable severity accompanied by schistocytosis on blood smear, and markedly elevated LDH.
2. Thrombotic thrombocytopenic purpura.
   a. Clinical features: microangiopathic anemia, thrombocytopenia, end-organ damage (e.g., renal, central nervous system [CNS], cardiac).
   b. Risk factors: HIV, lupus, congenital.
   c. Diagnostic testing.
      i. Blood smear with corroborative clinical features.
      ii. Very low levels of ADAMTS13 specific, but often not immediately available.
   d. Therapy: plasma exchange ± corticosteroids.
3. Hemolytic uremic syndrome.
   a. Clinical features: microangiopathic anemia, thrombocytopenia, renal failure.
   b. Risk factors: preceding enterohemorrhage *Escherichia coli* gastroenteritis.
   c. Diagnostic testing.
      i. Blood smear with corroborative clinical features.
      ii. Levels of ADAMTS13 often normal.
   d. Therapy.
      i. Supportive care.
      ii. Value of plasma exchange uncertain, but may be performed for severe cases.

TABLE 92-1 Drug-Induced Hemolytic Anemia

Mechanism	Hapten	Ternary complex	Autoantibody	Unknown
Description	Drug directly binds to the RBC membrane	Drug–antibody complex binds to RBC	Alters immune system function, production of autoantibodies	Unknown
Associated drugs	Penicillin	Amphotericin B	Cephapirin	Chlorpromazine
	Cephalosporin	Cefotaxine	Tolmentin	Melphalan
	Tetracycline	Ceftriaxone	Nomifensine	Isoniazid
	Ampicillin	Cephalosporins	Methyldopa	Acetaminophen
	Methicillin	Chlorpropamide	Levodopa	Thiazides
		Chlorpromazine	Mefenamic acid	Ibuprofen
		Carboplatin		Erythromycin
		Diclofenac		
		Doxepin	Teniposide	Sulindac
		Hydrochlorothiazide	Procainamide	Omeprazole
		Fenoprofen	Diclofenac	Sulfa drugs
		Isoniazid		Rifampin
		Melphalan		Tricyclic antidepressants
		Nomifensine		
		Probenecid		
		Quinidine		
		Quinine		
		Probenecid		
		Rifampin		
		Tetracycline		
		Thiopental		
		Tolmentin		

RBC, red blood cell.

4. HELLP (*h*emolysis *e*levated *l*iver function *l*ow *p*latelet) syndrome.
   - **a.** Clinical presentation: microangiopathic anemia in mid- or late pregnancy, accompanied by elevation of liver transaminases and thrombocytopenia.
   - **b.** Risk factors: previous pregnancy, advanced maternal age, and preeclampsia.
   - **c.** Diagnostic testing: nonspecific (i.e., clinical diagnosis).
   - **d.** Therapy: prompt delivery and supportive care.

5. Malignant hypertension.
   a. Hematologic picture: microangiopathic anemia with mild-to-moderate thrombocytopenia, severe hypertension.
   b. Risk factors: scleroderma.
   c. Diagnostic testing: nonspecific (i.e., clinical diagnosis).
   d. Therapy: treat hypertension.
6. Cardiac valvular disease.
   a. Hematologic picture: microangiopathic anemia in patient with history of mitral repair.
   b. Risk factors: recent valvular repair (in last 6 to 12 months).
   c. Diagnostic testing: demonstration of mitral regurgitant jet.
   d. Therapy: valvular repair, afterload reduction

C. Paroxysmal nocturnal hemoglobinuria (see Chapter 91, section III).

1. Clinical features.
   a. Acute episode(s) of (recurrent) hemolysis.
   b. Markedly elevated LDH.
   c. Thrombosis in unusual locations (e.g., portal or hepatic vein, cerebral venous circulation).
2. Risk factors: may have concurrent bone marrow failure of variable severity.
3. Diagnostic test: flow cytometry demonstrates loss of glycosylphosphatidylinositol-anchored proteins (such as CD59) on leukocytes and erythrocytes.
4. Therapy.
   a. Anticoagulation (due to high risk of recurrence).
   b. Complement C5 inhibitor eculizumab can suppress hemolysis.

VI. INHERITED HEMOLYTIC ANEMIAS

A. Sickle cell disease.

1. Clinical presentation: chronic hemolytic anemia, episodes of painful sickle crises, chronic and acute lung disease.
2. Risk factors (for crises): infection, hypoxia.
3. Diagnostic testing: blood smear showing sickle cells; hemoglobin electrophoresis showing presence of hemoglobin S.
4. Therapy (for crises).
   a. Acute—pain control, oxygen, hydration, transfusion for severe anemia.
   b. Chronic—hydroxyurea for patients with more than three painful crises/year.
5. Complications.
   a. Chest crisis—acute respiratory disease/failure with severe hypoxemia; therapy is red cell exchange.
   b. Aplastic crisis—acute infection with parvovirus B19 leads to suppression of cytopoiesis; therapy is transfusion.
   c. Megaloblastic crisis—due to folate deficiency; therapy is administration of folate.

TABLE 92-2 Drugs that May Precipitate a Hemolytic Crisis in G6PD Deficiency

Acetanilid
Furazolidone
Nalidixic acid
Naphthalene
Isobutyl nitrate
Sulfamethoxazole
Phenazopyridine
Nitrofurantoin
Sulfacetamide
Sulfanilamide
Methylene blue
Phenylhydrazine
Sulfapyridine
Primaquine
Pamaquine
Dapsone
Quinolones

B. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.

1. Clinical presentation: acute onset of severe anemia and abrupt hemolysis.
2. Risk factors: ingestion of oxidative drugs by patients with G6PD deficiencies. Patients of Mediterranean descent are more at risk of severe and prolonged hemolysis than are individuals of African descent.
3. Diagnostic testing: G6PD levels.
   a. Can be falsely normal during episodes of acute hemolysis.
4. Therapy: supportive care, avoidance of suspect drugs (Table 92-2).

C. Membrane defects.

1. Clinical presentation: variable and chronic hemolytic anemia (typically mild to moderate).
2. Risk factors (for acute episodes of hemolysis): hemolysis can acutely worsen with infections.
3. Diagnostic testing: blood smear (Table 92-3).
4. Therapy: transfusion for acute severe anemia; splenectomy for chronic severe disease.

VII. NUTRITIONAL DEFICIENCIES

A. Iron.

1. Clinical presentation: microcytic anemia, concurrent thrombocytosis if severe.
2. Risk factors: chronic bleeding, gastric surgery, heavy periods.

TABLE 92-3 Findings on Peripheral Blood Smear and Associated Diseases

Finding	Associated disorder(s)
Microcytosis	Iron deficiency Thalassemia Anemia of inflammation (30% of cases)
Hypochromia	Same as microcytosis
Anisocytosis	Nonspecific finding
Poikilocytosis	Nonspecific finding
Spherocytes	Autoimmune hemolytic anemia Hereditary spherocytosis
Elliptocytosis	Iron deficiency, hereditary elliptocytosis
Target cells and concurrent microcytosis	Iron deficiency Thalassemia
Target cells and concurrent macrocytosis	Liver disease
Schistocytes	Microangiopathic hemolytic anemia
Ovalomacrocytosis	B_{12} or folate deficiency Myelodysplastic syndromes
Burr cells	Liver disease Kidney disease
Spur cells	Severe liver disease

3. Diagnostic testing.
   a. Low ferritin (>100 mg/L rules out iron deficiency).
4. Therapy: oral or (refractory cases) IV iron.

B. Folate.

1. Clinical features: macrocytic anemia, hypersegmented neutrophils, pancytopenia if severe.
2. Risk factors: poor nutrition, alcohol use.
3. Diagnostic test: high homocystiene level.
4. Therapy: oral folate (1 mg/day).

C. Vitamin B_{12}.

1. Hematologic picture: macrocytic anemia, hypersegmented neutrophils, pancytopenia if severe.
2. Risk factors: pernicious anemia, gastric or bowel surgery (including gastric bypass).
3. Diagnostic testing.
   a. Low vitamin B_{12} level.
   b. Elevated methylmalonic acid level.
4. Therapy.
   a. Oral vitamin B_{12}: 1 to 2 mg/day, or.
   b. Parenteral (intramuscular [IM]) B_{12}: 1 mg daily for 1 week, followed by weekly for 1 month, followed by monthly thereafter.

D. Copper.

1. Features: anemia and severe neutropenia; thrombocytopenia very rare.
2. Risk factors: gastric surgery, malnutrition, tube feedings.
3. Diagnostic testing.
   a. Low copper level.
4. Therapy: copper orally, 2 mg/day.

VIII. DISORDERS OF DECREASED RED CELL PRODUCTION

A. Anemia of inflammation (i.e., anemia of chronic disease).

1. Hematologic features: mild-to-moderate anemia; microcytic in one-third of cases.
2. Risk factors: may be secondary to infections, cancer, autoimmune disease, trauma, other entities.
3. Diagnostic testing.
   a. Low serum iron, low transferrin, normal or elevated ferritin.
   b. Inappropriately low erythropoietin for degree of anemia.
4. Therapy: therapy of underlying disease, transfusions; erythropoietin (see subsequent text).

B. Anemia of renal insufficiency.

1. Clinical presentation: anemia in the setting of renal disease.
2. Risk factors: renal disease—can be subtle in older patients.
3. Diagnostic testing: low erythropoietin, glomerular filtration rate (GFR) <60 mL/minute.
4. Therapy: erythropoietin replacement.

C. Aplastic anemia.

1. Hematologic picture: anemia with very low reticulocyte count and pancytopenia.
2. Risk factors: most often idiopathic.
3. Diagnostic testing.
   a. Low reticulocyte count (nonspecific).
   b. Bone marrow biopsy showing hypocellularity and reduced erythrocytic precursors.
4. Therapy: immunosuppression or bone marrow transplantation.

D. Pure red cell aplasia.

1. Hematologic features: anemia with very low reticulocyte count, but other cell lines normal.
2. Risk factors.
   a. Immunosuppressed patient—parvovirus B19.
   b. Drugs—phenytoin, azathioprine, isoniazid, valproic acid, and chlorpropamide.
3. Diagnostic testing.
   a. Bone marrow biopsy showing lack of red cell precursors.
   b. Polymerase chain reaction (PCR) for parvovirus B19.

4. Therapy.
   a. Discontinue offending agent.
   b. Immunoglobulin for parvovirus B19 infection.
   c. Immunosuppression for idiopathic cases.

E. α-Thalassemia.

1. Thalassemia minor (i.e., thalassemia trait).
   a. Hematologic features: mild microcytic anemia.
   b. Risk factors: African American or Asian.
   c. Diagnostic testing.
      i. Mild microcytic anemia with normal iron stores.
      ii. Hemoglobin electrophoresis generally normal.
      iii. Positive α-thalassemia mutational analysis.
   d. Therapy.
      i. None required.
      ii. Avoid inappropriate iron supplementation.
2. Hemoglobin H disease.
   a. Hematologic features: moderate hemolytic anemia.
   b. Risk factors: Asian background.
   c. Diagnostic testing.
      i. Microcytosis.
      ii. Erythrocytes with Heinz bodies.
   d. Therapy: severe cases may require splenectomy.

F. β-Thalassemia.

1. Thalassemia minor (i.e., thalassemia trait).
   a. Hematologic features: mild microcytic anemia.
   b. Risk factors: Mediterranean or Asian origin.
   c. Diagnostic testing.
      i. Hemoglobin electrophoresis showing increased Hgb A_2.
   d. Therapy: none required.
2. Thalassemia major.
   a. Hematologic features: severe microcytic anemia.
   b. Risk factors: Mediterranean or Asian origin.
   c. Diagnostic testing.
      i. Hemoglobin electrophoresis showing increased Hgb A_2.
   d. Therapy: chronic transfusion, stem cell transplantation if human leukocyte antigen (HLA)-matched sibling donor available.

G. Hemoglobin E.

1. Hematologic features: mild microcytic anemia.
2. Risk factors: Asian origin.
3. Diagnostic testing.
   a. Hemoglobin electrophoresis showing increased hemoglobin E.
4. Therapy: none.

H. Myelodysplasia.

1. Hematologic features: mild-to-severe macrocytic anemia, often other cytopenias (especially thrombocytopenia) present.

2. Risk factors: older age, previous exposure to chemotherapy or radiation.
3. Diagnostic testing.
   a. Bone marrow aspirate and biopsy demonstrating morphologic abnormalities of developing blood cells.
   b. Abnormal cytogenetics (in 40% to 70% of cases only).
4. Therapy.
   a. Must be individualized.
   b. May include RBC growth factors, transfusions, chemotherapy, and/or stem cell transplantation.

IX. DIAGNOSTIC APPROACH TO ANEMIA

A. Complete blood count (CBC).
   1. Evaluate RBC indices.
   2. Presence of other cell line abnormalities.
   3. With severe hemolysis/agglutination a non-automated hematocrit by centrifugation may be required.

B. Blood smear (Table 92-3).

C. Reticulocyte count.
   1. Measurement of "new" red cells.
      a. Surrogate marker for marrow erythropoietic activity.
      b. Absolute reticulocyte count.
         i. Normal range is approximately 35 to 90,000/μL.
         ii. Normal range assumes no anemia (i.e., represents physiologic erythropoiesis).
      c. Corrected reticulocyte count.
         i. Percent reticulocyte count multiplied by patient's hematocrit and then divided by 45.
   2. Interpretation of reticulocyte count.
      a. Decreased (<0.01% or <5,000/μL): indicates marrow aplasia or myelodysplasia.
      b. Normal (1%, 35 to 90,000/μL): may still represent the following:
         i. Production defect, as values should increase above the normal range in response to anemia.
      c. Increased (>3%, or >100,000/μL): characteristic of hemolysis or blood loss.

D. Additional testing as guided by items 1 to 3 above in conjunction with assessment of clinical factors.

X. THERAPY

A. Specific therapy (e.g., iron for iron deficiency).

B. Transfusion—see Chapter 93.

C. Erythropoietin.
   1. Clearest indications for use.
      a. Renal failure/insufficiency (e.g., dialysis dependent).
      b. Use in other settings may be considered.

i. For example, myelodysplasia with refractory anemia and baseline erythropoietin level <200 to 500 mIU/mL.

c. Studies of erythropoietin use in patients in the ICU have not shown benefit in preventing transfusions when a restrictive transfusion protocol is followed.

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93 Transfusion Therapy: Blood Components and Transfusion Complications

Suchitra Pandey and Ashok Nambiar

I. RED BLOOD CELLS (RBCs)

A. General principles.

1. Manufacture and contents.
   - **a.** Obtained by apheresis collection or prepared from anticoagulated (citrated) whole blood. Following centrifugation, plasma is removed and additive solution is added.
   - **b.** Each unit of packed red blood cells (pRBCs): approximately 200 mL; residual plasma: <50 mL; hematocrit: 55% to 60%.

B. Indications.

1. Augment O_2-carrying capacity in anemic patients.
2. Evidence-based guidelines for hemoglobin (Hgb) thresholds for transfusion.
   - **a.** The TRICC (Transfusion Requirements in Critical Care) trial showed that a restrictive red cell transfusion strategy (transfusion trigger of <7 g/dL) was at least as effective as, and possibly superior to, a more liberal strategy (transfusion trigger of <10 g/dL) in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.
   - **b.** The FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) trial showed that even in elderly patients with underlying cardiovascular disease/risk factors, it is reasonable to limit transfusions for symptoms of anemia or a Hgb level of < 8g/dL.

C. Dose, administration.

1. A pRBC unit typically raises Hgb by approximately 1 g/dL in an adult patient.

D. Special requests: see Table 93-1.

II. PLATELETS

A. General principles.

1. Manufacture and contents.
   - **a.** Platelet concentrates (PCs).
     - **i.** Prepared from whole blood by centrifugation.

TABLE 93-1 Requests for Special Red Cell and Platelet Products

Request/ modification	Description	Indications
Irradiation	Gamma-irradiation (25 Gy) inhibits proliferation of lymphocytes—preventing transfusion-associated graft-versus-host disease	Congenital/acquired immunodeficiency Hematologic malignancies Stem cell transplantation HLA-matched products, transfusions from relatives, and granulocyte products Fetus/neonate
CMV negative	Blood donor is negative for CMV antibodies	Immunosuppressed patients and pregnant women who are CMV seronegative Fetus/neonate
Leukocyte reduced[a]	Prestorage filtration removes >99.9% of WBCs (residual white cell count $<5 \times 10^6$ WBCs)	Same as CMV negative Frequently transfused patients (reduces HLA alloimmunization) Recurrent febrile reactions
Washing[b]	Removes >98% of plasma proteins and electrolytes	Recurrent or severe allergic/febrile reactions; severe IgA deficiency; risk of hyperkalemia
Volume reduction[c]	Centrifugation and removal of >50% of supernatant plasma	Circulatory overload Recurrent allergic reactions

[a]Leukoreduced products are considered equivalent to CMV-negative products. Breakthrough infection rates of 1%–2% for CMV-seronegative products and 2% to 3% for leukoreduced products have been reported.
[b]Washing RBC units causes a 20% loss of red cells. Washing platelets causes both platelet loss and dysfunction.
[c]Volume reduction of platelets results in less platelet loss/dysfunction than washing platelets.

ii. Five to six PCs (each containing approximately 5.5×10^{10} platelets) are pooled to obtain an adult dose (approximately 300 mL).

b. Apheresis platelets.

i. Collected from single donors; comprise 80% to 90% of platelets transfused in the United States.

ii. Contain approximately 3×10^{11} platelets in 200 to 400 mL plasma; equivalent to a pool of 6 PCs (6-pack).

B. Indications.

1. Active bleeding: patients with low platelet counts or platelet dysfunction.
2. Prophylactically.
   a. Platelet counts <10,000 /μL: stable hematological disease.
   b. Platelets counts <20,000/μL: fever or mucositis.

c. Platelet counts <50,000/μL: invasive procedures.
d. Platelet counts <100,000/μL: neurosurgery, intracranial bleeding.

3. Platelet transfusions are generally avoided in patients with thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, and idiopathic thrombocytopenic purpura.

C. Dose, administration.

1. One apheresis platelet unit typically raises platelet counts by 30,000 to 60,000/μL.
2. Suspect platelet refractoriness if 10- to 60-minute posttransfusion counts show poor increments.
   a. Refractoriness due to antibodies against human leukocyte antigen (HLA) and/or platelet-specific antigens requires transfusion of cross-matched or HLA-matched platelets.
   b. Nonimmune causes include hypersplenism, fever, and active bleeding.

D. Special requests: see Table 93-1.

III. FRESH FROZEN PLASMA (FFP/FP24)

A. General principles.

1. Manufacture and contents.
   a. Obtained by apheresis or separation of plasma from centrifuged whole blood.
   b. One unit (approximately 200 mL) contains approximately 1 international unit/mL of each coagulation factor and 400 mg of fibrinogen.

B. Indications.

1. Multiple coagulation factor deficiency.
   a. International normalized ratio (INR) >1.5: active bleeding/invasive procedures.
2. Dilutional coagulopathy.
3. Deficiency of single coagulation factors, protein C, or protein S, when specific concentrates are unavailable.
4. Emergent reversal of warfarin.
5. FFP should not be used to "correct" mild elevations in INR/partial thromboplastin time (PTT).

C. Dose, administration.

1. A dose of 10 to 20 mL/kg increases factor levels by 20% to 30% soon after infusion.

IV. CRYOPRECIPITATE

A. General principles.

1. Manufacture and contents.
   a. Cold-insoluble protein that precipitates when FFP is thawed to 1°C to 6°C.

b. Each unit (approximately 15 mL) contains approximately 250 mg fibrinogen; 80 international units each of factor VIII and von Willebrand Factor (vWF) and 40 to 60 international units of factor XIII.

B. Indications.

1. Dilutional coagulopathy, disseminated intravascular coagulation (DIC), or dysfibrinogenemia.
2. Factor XIII deficiency.
3. Uremic patients with platelet dysfunction refractory to dialysis and desmopressin (DDAVP) therapy.

C. Dose, administration.

1. A pool of 10 units increases fibrinogen by approximately 50 mg/dL in adults.

V. TRANSFUSION RISKS

A. General principles.

1. Transfusion-associated infections (see Table 93-2).
2. Acute hemolytic transfusion reaction (AHTR).
a. ABO-incompatible RBCs lysed by preexisting antibodies in recipient plasma or isoagglutinins in transfused plasma products lyse recipient RBCs.
b. Signs/symptoms: Fever, rigors, flank or infusion site pain, vomiting, dyspnea, hypotension, hemoglobinuria, renal failure, and DIC.
c. Mechanical damage and hemolysis resulting from malfunctioning blood warmers or extracorporeal circuits, or from addition of medications or hypotonic solutions to RBC units, usually have a benign clinical course.
d. Stop transfusion immediately. Check patient's identity with identifiers on blood bag. Send product and posttransfusion sample to blood bank for hemolysis workup, which includes a direct Coombs test.
e. Therapy: aggressive hydration; cardiopulmonary and renal support. Monitor for DIC.

3. Delayed hemolytic transfusion reaction.
a. RBC lysis by a newly formed antibody or rising levels of a previously undetectable antibody.
b. Asymptomatic or fever, jaundice, drop in hematocrit approximately 3 to 14 days following transfusion.
c. Transfusion requirement: antigen-negative, crossmatch-compatible RBCs.

4. Transfusion-related acute lung injury (TRALI).
a. Incidence: Approximately 1 in 12,000 transfusions. Number one cause of transfusion-related fatality in the United States.
b. Severe hypoxemia (PaO_2:FIO_2 < 300) and radiological evidence of pulmonary edema occurring during or within 6 hours of transfusion in patients without evidence of left atrial hypertension.
c. HLA class I and II antibodies, antineutrophil antibodies, and biologically active lipids have been implicated.

TABLE 93-2 Transfusion-Transmitted Infectious Risks

Infectious agent	Risk per unit transfused	Screening in US donors
HIV-1/2	1 in 1.5 million[a]	Anti-HIV 1/2, nucleic acid testing (NAT) for HIV-1
Hepatitis C	1 in 1.2 million[a]	Anti-HCV, NAT
Hepatitis B	1 in 300,000[a]	HBsAg, anti-HBc, NAT
HTLV-I/II	1 in 2.7 million[a]	Anti-HTLV I/II
CMV	Infrequent with leukoreduced or CMV-negative products	Anti-CMV
West Nile Virus (WNV)	Rare	NAT
Trypanosoma cruzi	Rare	Anti-T.cruzi
Babesia	Increased risk in endemic regions, and, during summer months[b]	No FDA-approved donor screening test, is currently available
Malaria, other parasites	Rare	Donors deferred for high risk travel
Bacterial sepsis	RBC: 1 in 250,000; Platelet: 1 in 75,000 to 200,000	All platelets are screened for bacterial contamination[c]

[a]Risk per unit represents window-period residual risk. The window periods for HIV, HCV, HBsAg, and HTLV are 9.1, 7.4, 38, and 51 days, respectively.
[b]Rate of transfusion-transmitted Babesia (TTB) has been reported as 1 in 1,800 to 100,000 RBC units transfused in Connecticut and 1 in 15,000 RBC units transfused in Rhode Island. Since 2005, 12 fatalities from TTB have been reported to the FDA. TTB should be considered in blood product recipients with unexplained fever and hemolytic anemia.
[c]Apheresis platelets are screened by culture. PCs are screened by either culture or a point of issue test.

d. Rule out cardiogenic pulmonary edema and other causes of acute lung injury.

e. Therapy: Rapid and intensive respiratory support. TRALI usually resolves in 72 to 96 hours.

5. Transfusion-associated circulatory overload (TACO).

a. Incidence: TACO has been reported in <1% to up to 8% of transfusions depending on the patient population.

b. Risk factors: Increased age, left ventricular dysfunction, renal failure, recent surgery, and mechanical ventilation. A prospective cohort study in intensive care unit patients reported that greater transfusion volume, plasma transfusion, a positive fluid balance, and increased infusion rate were risk factors for TACO.

c. Signs/symptoms: Dyspnea, pulmonary edema on chest x-ray, increased central venous or pulmonary arterial wedge pressures, elevated B-type natriuretic peptide (BNP) levels.

d. Therapy: Stop transfusion. Provide supplementary oxygen; begin intravenous (IV) diuresis; and reassess fluid balance. In patients with risk factors, transfuse each unit slowly, but within 4 hours.

6. Febrile nonhemolytic transfusion reaction (FNHTR).
- **a.** Fever (defined as an increase in temperature ≥ 1°C) or chills/rigors during or immediately after transfusion.
- **b.** Mainly due to cytokines, which can accumulate during storage of cellular products.
- **c.** Stop transfusion; rule out hemolytic transfusion reaction and bacterial contamination by appropriate testing (AHTR workup; Gram stain/culture of product).
- **d.** Fever and rigors respond to antipyretics and Meperidine, respectively.

7. Allergic transfusion reaction.
- **a.** Hypersensitivity reactions due to allergens and/or allergic agonists in the component.
- **b.** Mild reactions (hives, urticaria): Stop transfusion; administer antihistamines. Resume transfusion only if symptoms are mild and abate with medications.
- **c.** Severe/anaphylactic reactions: Stop transfusion; administer antihistamines, steroids, fluids, and vasopressors as needed. Premedicate with antihistamines and steroids for future transfusions. Washing RBCs or volume-reducing platelets may minimize reactions.
- **d.** Severely immunoglobulin A (IgA)-deficient patients (IgA < 0.05 mg/dL) with anti-IgA antibodies are at risk for anaphylactic transfusion reactions. Cellular products must be extensively washed.

8. Citrate toxicity.
- **a.** Occurs in the setting of massive transfusion or large-volume cytapheresis/plasmapheresis.
- **b.** Signs/symptoms: Perioral and digital paresthesias and nausea. Rarely, symptomatic hypocalcemia can lead to tetany and cardiac arrhythmias.
- **c.** Therapy: Monitoring levels of ionized calcium and ionized magnesium; replacement as needed.

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94 The Leukemias

Karen K. Ballen

I. GENERAL PRINCIPLES

- **A.** Leukemias are curable with chemotherapy.
- **B.** Approximately 30% of adults with acute leukemia can be cured of disease.
- **C.** High-dose chemotherapy followed by allogeneic stem cell transplantation is a curative therapy for selected patients with leukemia; 40% to 50% chance of cure.
- **D.** Four types of leukemia:
  1. Acute lymphoblastic leukemia (ALL).
  2. Acute myelogenous leukemia (AML).
  3. Chronic lymphocytic leukemia (CLL).
  4. Chronic myelogenous leukemia (CML).

II. ETIOLOGY

- **A.** Most cases are idiopathic; no lifestyle risk factors.
- **B.** AML may arise as a result of prior chemotherapy or radiation therapy.
  1. Therapy-related AML has a poor prognosis.
  2. Associated with abnormalities of chromosome 5, 7, and 11.
- **C.** AML may arise from a prior myelodysplastic or myeloproliferative syndrome.

III. PATHOPHYSIOLOGY

- **A.** ALL more common in children, but can occur in adults.
  1. Can present with mediastinal mass.
  2. Can present with central nervous system (CNS) and testicular involvement.
- **B.** AML more common in adults.
  1. Monocytic variants can have skin, gum, and CNS involvement.
- **C.** Acute promyelocytic leukemia (APML).
  1. Associated with bleeding and disseminated intravascular coagulation (DIC).
- **D.** Chronic lymphocytic leukemia.
  1. Often indolent disease of elderly.
- **E.** Chronic myelogenous leukemia.
  1. Can progress to acute leukemia.
     - **a.** Myeloid blast crisis (70% of cases).
     - **b.** Lymphoid blast crisis (30% of cases).

IV. DIAGNOSIS

A. History.

1. Nonspecific symptoms of fatigue, shortness of breath, infection, bleeding.

B. Examination.

1. Pallor, petechiae, sometimes splenomegaly, or a flow murmur.

C. Laboratory studies.

1. Complete blood count.
   a. Anemia, thrombocytopenia; white blood cell (WBC) count may be normal, high, or low.

D. Peripheral blood smear.

1. Increased immature cells.

E. Bone marrow aspirate and biopsy.

1. Flow cytometry, cytogenetics, molecular studies.
2. Acute leukemia defined as >20% blasts.

F. Molecular diagnostic studies.

1. BCR-ABL mutation diagnostic of CML.
2. PML–RAR-α diagnostic of APML.
3. FLT3 mutation is a negative prognostic feature for AML.

V. TREATMENT

A. Acute lymphoblastic leukemia.

1. Induction chemotherapy with four to five chemotherapy drugs:
   a. Asparaginase, prednisone, vincristine, doxorubicin.
   b. CNS prophylaxis with intrathecal chemotherapy.
   c. Intensification and maintenance chemotherapy over 18 to 24 months (outpatient).
   d. Philadelphia chromosome–positive patients also receive tyrosine kinase inhibitor such as imatinib or dasatinib.
   e. Allogeneic transplantation in first remission for high-risk or young patients.
   f. Cure rate 90% for children, 50% for young adults, 15% over age 50.

B. Acute myelogenous leukemia.

1. Elderly patients have poor prognosis—consider supportive care with hydroxyurea, or outpatient treatment with 5-azacytidine or decitabine.
2. Induction chemotherapy with idarubicin and cytosine arabinoside (ARA-C).
3. Allogeneic stem cell transplantation for patients at high risk of relapse, often based on cytogenetics.
4. Cure rate 70% with favorable subtypes, 30% with higher risk, 10% over age 60.

C. Acute promyelocytic leukemia.

1. Cure rate of >90%.
2. Over 5% of patients die of bleeding before diagnosis can be made.
3. Prompt diagnosis and treatment are essential.

4. All-*trans*–retinoic acid (ATRA) plus chemotherapy.
5. Consolidation with ATRA, daunorubicin, and arsenic.

D. Chronic lymphocytic leukemia.

1. Observation until disease progression, often many years.
2. Fludarabine- or bendamustine-based therapy.
3. Alemtuzumab or allogeneic stem cell transplantation for refractory patients.
4. Long natural history, but transplant only known curative therapy.

E. Chronic myelogenous leukemia.

1. Oral tyrosine kinase inhibitor—imatinib, dasatinib, or nilotinib.
2. Long natural history with tyrosine kinase inhibitors, not clear if patients cured.

VI. COMPLICATIONS

A. Leukostasis.

1. Most likely when the blast count > 50,000/mm^3.
2. Can occur even with lower WBCs.
3. Most common in AML because blasts are large.
4. Hypoxia, pulmonary infiltrates, visual changes, mental status changes, CNS bleeding.
5. Treatment for leukostasis.
   a. Intravenous fluids.
   b. Prompt initiation of chemotherapy.
   c. Hydroxyurea 1 to 2 g PO twice daily to lower WBCs.
   d. Leukapheresis.
   e. Avoid red blood cell (RBC) transfusions, which increase viscosity.

B. Bleeding.

1. Thrombocytopenia.
   a. Increased risk CNS bleed when platelet count < 10,000/mm^3.
   b. Platelet transfusion when platelet count < 10,000/mm^3 or bleeding.
   c. Irradiated, filtered blood products only.
   d. Human leukocyte antigen (HLA)–matched platelets if alloimmunized.
   e. No family member donations if patient a transplant candidate.
2. Disseminated intravascular coagulation.
   a. Common with APML, but can also be seen in AML/ALL.
   b. Life-threatening bleeding, stroke, CNS bleed.
   c. Treat with fresh frozen plasma, platelets, and cryoprecipitate for fibrinogen < 100.
   d. If APML or suspected APML, start ATRA promptly.

C. Infections.

1. General principles.
   a. WBCs may be high, but abnormal WBC function—patient functionally neutropenic.
   b. Chemotherapy suppresses the immune system.
   c. Imaging procedures such as computed tomographic (CT) scans may help guide coverage; consider bronchoscopy for pulmonary infiltrates.

2. Bacterial infections.
   a. Gram-positive infections related to indwelling catheters.
   b. Gram-negative infections related to a damaged intestinal tract.
3. Fungal infections.
   a. Increased with neutropenia, antibiotics, indwelling catheters, parenteral nutrition, and steroids.
   b. *Candida* (skin, liver, esophagus).
   c. *Aspergillus* (lung, sinuses).
4. Viral infections.
   a. Herpes simplex virus, herpes zoster.
   b. Influenza, respiratory syncytial virus serious infections in leukemia patients.
5. Other infections.
   a. Pneumocystis pneumonia (PCP) seen in ALL patients receiving steroids.
6. Treatment of infections.
   a. Treat fever immediately as presumptive infection.
   b. Coverage for gram-negative infections, including *Pseudomonas*.

TABLE 94-1 Side Effects of Common Chemotherapy Drugs

Drug	Alopecia	Nausea/ vomiting	Bone marrow suppression	Other
Cytosine arabinoside (ARA-C)	+	+	++	Fever, renal failure, cerebellar toxicity
Idarubicin, daunorubicin	++	++	++	Cardiac, mucositis, vesicant
Etoposide	+	+	+	Hypotension
All *trans* retinoic acid (ATRA)	–	–	–	Increased WBCs
	–	–	–	Lung infiltrates
Cyclophosphamide (Cytoxan)	+	++	++	Hemorrhagic cystitis
Prednisone	–	–	–	Muscle weakness, edema, glucose intolerance
Vincristine	–	+	–	Neuropathy
Asparginase	–	–	–	Pancreatitis, coagulopathy
Imatinib (Gleevec)	–	–	+	Elevated liver tests, rash
Fludarabine	–	+	–	Increased risk late infection

+, mild toxicity; ++, moderate-to-severe toxicity; –, ATRA toxicity.

c. Persistent fever, coverage for gram-positive infections and fungus.
d. Preventative regimens include gram-negative coverage (quinolone), antifungal coverage (fluconazole), and PCP coverage (in ALL patients).

7. Tumor lysis syndrome.
a. Rapid destruction of tumor cells.
b. High uric acid, low calcium, high potassium.
c. Can progress to acute renal failure with fatal hyperkalemia.
d. Prevention of tumor lysis syndrome.
i. Hydration before chemotherapy.
ii. Allopurinol or rasburicase.

D. Pulmonary toxicity.

1. Acute lung toxicity from fludarabine, cytarabine, bortezomib, rituximab, all-*trans*–retinoic acid <5%.
2. Late lung toxicity (pulmonary fibrosis) from busulfan, bleomycin, BCNU, melphalan <5%.
3. Acute leukemia itself can present with pulmonary infiltrates—often respond to steroids.
4. Chemotherapy toxicity—see Table 94-1.

SUGGESTED READINGS

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95 Oncologic Emergencies

Diane M.F. Savarese

I. SUPERIOR VENA CAVA (SVC) SYNDROME

A. Etiology.

1. SVC syndrome results from obstruction of venous return.
- **a.** Invasion of tumor into SVC or intravascular thrombus.
- **b.** External compression of the SVC.

2. Sixty-five percent to eighty percent of cases due to malignancy.
- **a.** Predominantly lung cancer and lymphoma.

3. Other causes.
- **a.** Thrombosis (usually with an indwelling intravascular device).
- **b.** Mediastinal fibrosis.

B. Clinical features and diagnosis.

1. Symptoms and signs of SVC syndrome (Table 95-1) are related to the following:
- **a.** Poor venous return.
- **b.** Increased intravenous (IV) pressure.
- **c.** Collateral vessel engorgement.

2. Radiographic studies are usually diagnostic.
- **a.** Chest radiograph abnormal in >80%: mediastinal widening, pleural effusion.
- **b.** Contrast-enhanced chest computed tomography (CT) the preferred diagnostic study.
  - **i.** Identifies the site of venous obstruction.
  - **ii.** Suggests etiology and identifies impending complications.
- **c.** Upper extremity venography.
  - **i.** Gold standard for defining the level and extent of SVC obstruction.
  - **ii.** Cannot identify etiology unless thrombosis is the sole cause.

3. Tissue diagnosis: Routine diagnostic procedures carry little excess risk.
- **a.** Pursue the least invasive option.
  - **i.** Sputum or pleural fluid cytology.
  - **ii.** Biopsy of an enlarged peripheral lymph node.
  - **iii.** Transthoracic CT-guided biopsy.
  - **iv.** Bronchoscopy with biopsy.
- **b.** Pursue more invasive procedure if necessary to establish diagnosis.
  - **i.** Mediastinoscopy.
  - **ii.** Video-assisted thoracoscopy.
  - **iii.** Thoracotomy.

TABLE 95-1 Common Symptoms and Signs of Superior Vena Cava Syndrome

Symptom or sign	Percentage of all patients (range)
Hemodynamic	
Facial edema	82 (60–100)
Arm edema	46 (14–75)
Distended neck veins	63 (27–86)
Distended chest veins	53 (38–67)
Facial plethora	20 (13–23)
Visual symptoms	2
Respiratory	
Dyspnea	54 (23–74)
Cough	54 (38–70)
Hoarseness	17
Stridor	4
Neurologic	
Syncope	10 (8–13)
Headache	9 (6–11)
Dizziness	6 (2–10)
Confusion	4
Obtundation/cerebrovascular event	2

Data from Armstrong BA, Perez CA, Simpson JR, et al. Role of irradiation in the management of superior vena cava syndrome. *Int J Radiat Oncol Biol Phys* 1987;13:531–539; Yellin A, Rosen A, Reichert N, et al. Superior vena cava syndrome: the myth - the facts. *Am Rev Respir Dis* 1990;141:1114–1118; Schraufnagel DE, Hill R, Leech JA, et al. Superior vena caval obstruction—is it a medical emergency? *Am J Med* 1981;70:1169–1174; Chen JC, Bongard F, Klein SR, et al. A contemporary perspective on superior vena cava syndrome. *Am J Surg* 1990;160:207–211; Rice TW, Rodriguez RM, Barnette R, et al. Prevalence and characteristics of pleural effusion in superior venal caval syndrome. *Respirology* 2006;11:299–305; and Urruticoechea A, Mesía R, Domínguez J, et al. Treatment of malignant superior vena cava syndrome by endovascular stent insertion. Experience on 52 patients with lung cancer. *Lung Cancer* 2004;43:209–214.

c. Emergent treatment before pursuing histologic diagnosis required if the following are present:
i. Stridor.
ii. Confusion, obtundation.
iii. Hemodynamic compromise.

C. Treatment.

1. Goals: Alleviate symptoms; treat underlying cause.
a. Urgency of treatment depends on severity of SVC syndrome (Yu, 2008). In the presence of the following severe life-threatening symptoms, perform immediate venogram and urgent endovascular stenting for rapid relief of symptoms; direct thrombolysis if thrombus present:
i. Stridor.
ii. Confusion, obtundation.
iii. Hemodynamic compromise.

b. After urgent management of severe or life-threatening symptoms, and for all others, establish the histologic diagnosis and tumor stage to select appropriate therapy for malignancy-associated SVC syndrome.

2. Definitive therapy depends upon underlying etiology.

a. Malignant cause: Histology and tumor stage dictate initial antitumor treatment.

i. Surgery for selected cases (nonmetastatic thymoma, residual germ cell cancer).

ii. For nonsurgically managed malignancy, chemotherapy is preferred for chemosensitive tumors (lymphoma, mediastinal germ cell tumor, small cell lung cancer).

iii. Intraluminal stenting.

(a) Useful for extrinsic tumor compression.

(b) Provides more rapid relief of symptoms in more patients than radiation therapy (RT).

(c) Does not compromise ability to establish a histologic diagnosis.

iv. Radiation therapy.

(a) Relieves symptoms, though not as quickly as stenting.

b. Nonmalignant causes.

i. Intravascular device associated.

(a) Remove device, if possible.

(b) Consider thrombolysis if thrombus ≤5 days old.

ii. Mediastinal fibrosis.

(a) Benefits of stenting are generally short lived.

(b) Surgical bypass may be required.

3. Supportive care.

a. Bed rest with head elevated to reduce central venous pressures.

b. Diuretics (avoid depletion of intravascular volume), decreased salt intake.

c. Oxygen.

4. Glucocorticoids.

a. Most useful in lymphoma and thymoma (cytolytic effect).

b. Short course of high-dose glucocorticoids may be recommended with emergent RT for impending airway obstruction.

i. Minimizes edema.

ii. Reduces the risk of central airway obstruction.

II. TUMOR LYSIS SYNDROME (TLS)

A. Pathophysiology.

1. Massive cytolysis of malignant cells releases large amounts of potassium, phosphate, and uric acid with secondary hypocalcemia.

2. Acute renal failure from precipitation of uric acid and/or calcium phosphate in the renal tubules.

B. Etiology.

1. Most commonly encountered after initial chemotherapy for the following:
   a. Clinically aggressive non-Hodgkin lymphomas (NHL, particularly the Burkitt and lymphoblastic subtypes).
   b. Acute lymphoblastic leukemia (ALL).
2. May also occur spontaneously in high-grade NHL or ALL.
3. May occur in other tumor types with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy.

C. Diagnosis.

1. Cairo-Bishop definition (Table 95-2).

D. Prevention and treatment.

1. Best management is prophylaxis. Risk stratification guidelines are available (Cairo et al., 2010).
2. Prevention.
   a. Aggressive IV hydration (2 to 3 $L/m^2/d$) with diuresis to enhance washout of uric acid crystals.
   b. Limit phosphate and potassium intake during initial therapy.
   c. Administration of hypouricemic agent(s).
      i. Allopurinol for low- and intermediate-risk disease (Cairo et al., 2010).
      ii. Rasburicase (recombinant urate oxidase) for high-risk disease.
         (a) Burkitt or lymphoblastic lymphoma, Burkitt–ALL, or other ALL with a white blood cell (WBC) count ≥100 × 10^9/L, and other high-risk lymphomas with a high lactate dehydrogenase (LDH) or advanced stage, or other patients if uric acid ≥8 mg/dL (Cairo et al., 2010).
         (b) Rasburicase contraindicated in G6PD deficiency.

TABLE 95-2 Cairo-Bishop Definition of Tumor Lysis Syndrome

Laboratory TLS

Abnormalities in two or more of the following serum values, present within 3 days before, or 7 days after instituting chemotherapy:
Uric acid ≥ 8 mg/dL (476 μmol/L) or 25% increase from baseline
Potassium ≥ 6.0 mmol/L or 25% increase from baseline,
Phosphate ≥ 6.5 mg/dL (2.1 mmol/L) in children, or ≥4.5 mg/dL (1.45 mmol/L) in adults, or 25% increase from baseline
Calcium ≤ 7 mg/dL (1.75 mmol/L) or 25% decrease from baseline

Clinical TLS

Laboratory TLS plus one or more of the following:
Increased serum creatinine concentration (≥1.5 times the upper limit of normal [ULN])
Cardiac arrhythmia/sudden death
Seizure

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004;127:3.

d. Urinary alkalinization.
  i. Generally not recommended.
  ii. Benefit unproven; potential harms especially with hyperphosphatemia.
e. Monitoring during therapy.
  i. Closely monitor urine output, fluid balance, and serial assays of electrolytes, LDH, and serum uric acid.

3. Treatment of established TLS.
a. Aggressive hydration and diuresis, continuous cardiac monitoring, and measurement of electrolytes, creatinine, and uric cid every 4 to 6 hours.
b. Rasburicase if not given initially.
c. Treat specific electrolyte abnormalities, especially hyperkalemia.
d. Indications for renal replacement therapy.
  i. Severe oliguria or anuria.
  ii. Persistent hyperuricemia (rare with use of rasburicase).
  iii. Persistent hyperkalemia.
  iv. Hyperphosphatemia-induced symptomatic hypocalcemia.

III. EPIDURAL SPINAL CORD COMPRESSION (ESCC)

A. Pathophysiology.

1. Neoplastic mass in the epidural space with extrinsic compressesion of spinal cord.
a. Direct invasion from any of the following:
  i. Enlarging vertebral body metastases.
  ii. Retroperitoneal lymphadenopathy extending through the paravertebral neural foramina.
  iii. Intradural metastases.

2. Increased intradural pressure and vascular compromise lead to spinal cord infarction and rapid, irreversible loss of function.

B. Etiology.

1. Most common tumor types are lung, breast, prostate, kidney cancer, lymphoma, and myeloma.

C. Clinical presentation.

1. Back pain.
a. Initial symptom in >90% of patients.
b. Consider in any patient with known cancer (or symptoms suggesting the presence of undiagnosed cancer) and unexplained back pain.

2. Symmetric lower extremity weakness and hyperreflexia below the level of compression.
a. Lesions below the conus medullaris (cauda equina lesion) have weakness and depressed deep tendon reflexes in the legs.
b. Motor weakness occasionally progresses to paraplegia within hours.
c. Sensory deficits are rare initially, but usually develop at some point.
  i. The spinal sensory level, if present, is typically one to five levels below the level of compression.

ii. Saddle sensory loss is common with cauda equina lesions; higher lesions usually spare the sacral dermatomes.

3. Loss of bowel or bladder control is a late and poor prognostic sign.

D. Diagnosis.

1. Early diagnosis is essential; patients who begin treatment when paraplegic almost never regain ambulation.
2. Perform a thorough neurologic examination.
3. Obtain plain spine radiographs for evidence of the following:
   a. Pedicle loss.
   b. Vertebral compression fractures.
   c. Osteoblastic/osteolytic bone lesions.
   d. Major vertebral body collapse or pedicle erosion with a matching radiculopathy predicts a 75% to 83% chance of ESCC.
4. If either examination or x-rays are abnormal, a magnetic resonance imaging (MRI) or myelogram is necessary to exclude ESCC.
   a. MRI of the entire spine is preferred to assess location and extent of ESCC.
   b. CT myelography if timely MRI is unavailable or contraindicated.
5. Assess spine stability.
   a. Pain from an unstable spine will not be relieved with RT. An unstable spine must be stabilized either by surgical fixation or by percutaneous vertebral repair.
   b. A classification system for spinal stability based upon clinical and radiographic findings has been proposed (Fisher et al., 2010).

F. Treatment.

1. Pain management.
   a. Glucocorticoids: relieve pain within hours in most cases.
      i. Suggested regimen: dexamethasone 10 to 24 mg IV bolus followed by 16 to 24 mg orally daily in divided doses.
      ii. Higher initial doses (e.g., dexamethasone 100 mg) may enhance analgesia, but associated with more serious compications and no better neurologic outcomes.
   b. Opiates: most patients also require opiates to tolerate diagnostic studies.
2. Initial decompressive surgery.
   a. Consider for patients who are candidates for a surgical intervention, have a limited disease burden who have symptomatic progression during or following RT, need for spinal stabilization, or have a stable spine with high-grade ESCC and a relatively radioresistant neoplasm (e.g., melanoma, renal cell cancer).
3. Radiation therapy.
   a. Required following decompressive surgery.
   b. Treatment of choice: if aggressive radical resection is not feasible.
   c. External beam RT alone a reasonable alternative to surgery for patients with metastatic ESCC and a stable spine and radiosensitive neoplasm (breast cancer, lymphoma, myeloma), particularly if high disease burden and relatively poor prognosis.

d. Stereotactic radiosurgery should be considered for patients with a stable spine and a relatively resistant neoplasm (melanoma, renal cell cancer) who have no high-grade ESCC.

4. Chemotherapy.

a. Is recommended for selected chemoresponsive malignancies (e.g., small cell lung cancer, lymphoma).

IV. HYPERCALCEMIA OF MALIGNANCY

A. General principles.

1. Major metabolic abnormality in patients with cancer.

a. Occurs in 10% of patients.

2. Most common in breast, lung cancer; multiple myeloma.

B. Etiology and pathophysiology.

1. Develops through three mechanisms, all of which lead to increased osteoclast activation.

a. Osteolytic metastases.

b. Ectopic tumor production of parathyroid hormone–related protein (PTHrP).

i. Lung (squamous cell).

c. Direct bone invasion or local production of humoral factors (e.g., osteoclast-activating factor).

i. Multiple myeloma.

2. Consider coincident primary hyperparathyroidism.

a. Measure parathyroid hormone (PTH) in all hypercalcemic patients.

b. If serum PTHrP and PTH concentrations are both high, coexisting primary hyperparathyroidism probably present.

C. Clinical manifestations.

1. Symptoms and signs are most apparent when the rate of rise of serum calcium is rapid.

2. Change in mental status.

a. Can be subtle (e.g., lethargy or depression).

b. In the extreme, may include psychotic behavior, obtundation, and coma.

3. Cardiac arrhythmias.

a. Electrocardiographic (ECG) changes: prolonged PR and shortened QT interval.

b. *Digitalis*-toxic arrhythmias may develop more easily in hypercalcemic patients.

4. Renal consequences.

a. Polyuria followed by dehydration and prerenal azotemia.

b. Tubular damage from nephrocalcinosis (acidosis, glycosuria, hypomagnesemia, and aminoaciduria).

5. Gastrointestinal symptoms.

a. Anorexia.

b. Nausea and vomiting.

c. Constipation.
d. Abdominal pain.

D. Laboratory characteristics of hypercalcemia.

1. "Total serum calcium" not equivalent to "ionized calcium" (which represents biologically active calcium).
2. Approximately 40% of total serum calcium bound to protein (primarily albumin).
   a. Correct measured serum calcium in patients with hypoalbuminemia or hyperalbuminemia.
      i. One gram of albumin binds 0.8 mg of calcium; to calculate corrected total serum calcium value, add 0.8 mg/dL to the measured total serum calcium for each 1 g/dL decrease in serum albumin below 4.0 g/dL.
   b. In multiple myeloma, total serum calcium may be spuriously elevated, because hyperglobulinemia leads to increased binding of calcium; in such cases, ionized calcium should be measured.
3. Severity of hypercalcemia based on corrected total serum calcium level:
   a. Mild = 11 to 12 mg/dL (2.8 to 3 mmol/L).
   b. Moderate = 12 to 14 mg/dL (3 to 3.5 mmol/L).
   c. Severe = >14 mg/dL (>3.5 mmol/L).

E. Diagnosis.

1. Laboratory confirmation of hypercalcemia (see preceding text).
2. Many potential causes can be eliminated by the patient's history (Table 95-3).

TABLE 95-3 Differential Diagnosis of Hypercalcemia

Cancer
  With bone metastasis (solid tumor)
  Without bone metastasis (solid tumor)
  Hematologic (e.g., multiple myeloma, leukemia, lymphoma with bone involvement)
Primary toxic hyperparathyroidism
Thiazides
Milk-alkali syndrome
Vitamin D or A toxicity
Endocrine
  Thyrotoxicosis
  Adrenal insufficiency
  Pheochromocytoma (usually in association with primary hyperparathyroidism)
Granulomatous disease
  Tuberculosis
  Sarcoidosis (particularly immobilized patients with underlying bone disease)
Artifactual
  Hyperalbuminemia or hyper–gamma-globulinemia
  Venous stasis (prolonged tourniquet application)

F. Treatment.

1. Best treatment: specific therapy of the underlying malignancy.
2. Avoid thiazide diuretics, which promote renal tubular resorption of calcium.
3. Asymptomatic or mildly symptomatic (e.g., constipation) hypercalcemia (serum calcium ≤ 14 mg/dL) does not require immediate treatment. An acute rise to levels >12 mg/dL may cause marked changes in sensorium, requiring treatment. Patients with a serum calcium >14 mg/dL require treatment, regardless of symptoms.
4. Fluid replacement with normal saline.
   a. Most hypercalcemia patients are volume depleted.
   b. Initial rate of infusion: 150 to 300 mL/hour.
   c. Benefit usually temporary and insufficient to normalize the calcium level in most patients.
5. For euvolemic patients:
   a. Avoid further volume depletion.
   b. Furosemide: No clear evidence of benefit, and may cause harm by promoting diuresis and aggravating preexisting dehydration.
   c. Closely monitor total intake and output, weight, serum electrolytes, and urine electrolytes (at least within the first 12 hours).
6. Parenteral zoledronic acid.
   a. Treatment of choice.
   b. Dose = 4 mg over 15 minutes.
   c. Onset of action is within 24 hours.
7. Calcitonin.
   a. Consider if urgent need to decrease serum calcium (e.g., obtundation, ECG changes).
   b. Relatively weak effect; lowers serum calcium by a maximum of 1 to 2 mg/dL (0.3 to 0.5 mmol/L).
   c. Dose is 4 international units/kg IV administered subcutaneously or intramuscularly; onset of action is 4 to 6 hours; nasal calcitonin is ineffective.
      i. Doses can be increased up to 6 to 8 units/kg every 6 hours.
      ii. If a *hypo*calcemic response is seen in several hours, the frequency of dosing can be lengthened to every 6 to 12 hours.
   d. Tachyphylaxis limits efficacy to the first 48 hours, even with repeated doses.
7. Corticosteroids may be useful for patients with hematologic malignancies or breast cancer.
8. Gallium nitrate (200 mg/m^2 IV daily for 5 days) may be considered for refractory patients.
9. Hemodialysis.
   a. Treatment of last resort for severe hypercalcemia (serum calcium 18 to 20 mg/dL [4.5 to 5 mmol/L]).
   b. May be required in patients with renal failure.
10. In the absence of effective antineoplastic treatment, hypercalcemia typically recurs, and retreatment is required every 3 to 4 weeks.

V. MALIGNANT PERICARDIAL EFFUSION

A. Indicates a poor prognosis.

B. The most common primary tumor involving the pericardium is lung cancer; others include breast and esophageal cancer, melanoma, lymphoma, and leukemia.

C. Treatment (see Chapters 2 and 28).

1. Initial treatment is pericardiocentesis performed under echocardiographic guidance.
   a. After pericardiocentesis alone, fluid reaccumulates in as many as 60% of cases.
2. Measures to prevent reaccumulation.
   a. Prolonged drainage through intrapericardial catheter with or without intrapericardial instillation of sclerosing agents (e.g., bleomycin 30 to 60 units).
   b. Surgical management (e.g., pericardial window).
3. Systemic antitumor treatment for chemotherapy-responsive cancers (e.g., breast cancer, lymphoma).
4. RT is useful in a few selected cases.

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The authors delineate a system for classifying and grading the severity of clinical and laboratory TLS.

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SECTION 10

Pharmacology, Overdoses, and Poisonings

Luke Yip

96

Toxicology

Luke Yip

INTRODUCTION

This section focuses on the aspects of acute poisoning that are potentially life threatening or may lead to permanent organ damage and hence require immediate, usually intensive, medical care. This has been organized into a table to facilitate rapid access to concise toxicology information guiding management of acutely poisoned patients. The table is divided into four columns. The first column is alphabetically organized into either a specific agent (e.g., acetaminophen) or a class of agent (e.g., alcohol) with specific toxins (e.g., ethylene glycol, isopropanol, and methanol); individual agents appear alphabetically in the index. This is followed by a list of organ systems that can be targeted by the agent or its systemic effects. The second column focuses on action alerts, critical laboratory values, guidelines for clinical intervention, and the dosing of therapeutic drugs, antidotes, or antivenom. The third column lists adjunct therapy and extracorporeal treatments. The fourth column highlights caveats and potential complications. The content of this section is not a substitute for reference textbooks in intensive care medicine or medical toxicology, and does not address envenomations that usually occur outside of the United States. The interested reader is referred to the current edition of *Irwin and Rippe's Intensive Care Medicine* textbook and toxicology textbooks (e.g., *Goldfrank's Toxicologic Emergencies and Medical Toxicology*) for more detailed information on a given subject.

TABLE 96-1

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Acetaminophen (APAP) Acute: GI • Hepatotoxicity • FHF Neurologic • Encephalopathy • Coma and metabolic acidosis with serum APAP > 800 μg/mL (5,292 μmol/L) 4–12 h postingestion. GU • Oliguric renal failure 24–48 h with proteinuria, microscopic hematuria and back pain; usually proceeded by hepatotoxicity; non-oliguric renal failure is rare.	Serum APAP concentration above "treatment" line on acetaminophen toxicity (Rumack-Matthew) nomogram (Fig. 96-1): NAC • Oral: 140 mg/kg followed by 70 mg/kg every 4 h (dilute 3:1 with carbonated/fruit beverage for palatability); administer IV antiemetic (e.g., ondansetron 8 mg; Peds: 0.2 mg/kg, max 8 mg) and repeat the same oral dose if vomiting occurs within 1 h. OR • IV: 150 mg/kg in 200 mL D5W over 1 h followed by 50 mg/kg in 500 mL D5W over 4 h followed by 100 mg/kg in 1 L D5W over 16 h (6.25 mg/kg/h). NAC therapy may be terminated if the patient remains asymptomatic, serum APAP concentration below "treatment" line, *and* AST/ALT remains in the laboratory	Consider oral activated charcoal 1–2 g/kg in a cooperative patient presenting within 4 h of overdose. When to consider hemodialysis: Patient who present soon after an acute overdose, when NAC not available, no other options are available and hemodialysis can be expeditiously initiated; coma and metabolic acidosis with serum APAP >800 μg/mL (5,292 μmol/L); terminate when serum APAP <30 μg/mL (198 μmol/L) and acid–base disturbances are corrected.	The acetaminophen toxicity nomogram is valid following an acute single overdose of nonmodified release APAP occurring between 4 and 24 h; plots above "probable" and "high-risk" lines indicate 60% and 90% hepatotoxicity risk, respectively. NAC therapy: Anaphylactoid reactions; infusion volume in pediatric patients.

reference range at 20–24 h; continue NAC therapy (oral: every 4 h; IV 6.25 mg/kg/h) if patient's clinical condition deteriorates *or* AST/ALT becomes abnormal.

APAP/NAC-induced emesis: IV ondansetron 8 mg (Peds: 0.2 mg/kg, max 8 mg); metoclopramide 1–2 mg/kg.

Encephalopathy or FHF: IV NAC with the final infusion rate (6.25 mg/kg/h) until recovery or death.

Transfer to liver unit/ICU consideration: PT (measured in seconds) exceeds the time in hours after overdose, or INR >5.0 at any time, or metabolic acidosis, hypoglycemia, or renal failure.

OLT consideration:
- Consider listing for transplantation: Arterial lactate >3.5 mmol/L after fluid resuscitation.
- List for transplantation: Arterial pH <7.30 and lactate >3.0 mmol/L after fluid resuscitation.

OR

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Acetaminophen (APAP) Acute (*continued*)	PT/INR >100 s/>6.5, Cr >3.3 mg/dL (300 μmol/L), *and* encephalopathy grade ≥III within a 24-h period and normal arterial pH. Unreliable time of ingestion • Patient with signs and symptoms consistent with hepatotoxicity: NAC treatment same as above; continue NAC treatment (oral: every 4 h; IV 6.25 mg/kg/h) until clear clinical and laboratory evidence of improvement in patient's condition. If deterioration in clinical and laboratory status, consider parameters for referral to liver unit/ICU or OLT. • Asymptomatic patient with serum APAP concentration <10 mg/L (66 μmol/L) *and* AST/ALT within laboratory reference range: Repeat serum APAP level and AST/ALT in		

	6–8 h. If *both* normal, no further treatment for APAP overdose is needed. If *either* elevated, treat with NAC (same as above); NAC treatment may be terminated if the patient remains asymptomatic, serum APAP concentration <10 mg/L (66 µmol/L), *and* AST/ALT remains within or falls to the near upper limit of laboratory reference range at 20–24 h, otherwise continue NAC (oral: every 4 h; IV 6.25 mg/kg/h) until clear clinical and laboratory evidence of improvement or, if deterioration in clinical and laboratory status, consider parameters for referral to liver unit/ICU or OLT.	
Nonacute/repeated supratherapeutic ingestion: Same as Acetaminophen (APAP) "Acute"	Signs and symptoms consistent with hepatotoxicity: NAC treatment same as "Acute;" continue NAC until clear clinical and laboratory evidence of improvement; if deterioration in clinical and laboratory status, consider	Same as "Acute," except acetaminophen toxicity nomogram *not* valid at any time.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Non-acute/repeated supratherapeutic ingestion: Same as Acetaminophen (APAP) "Acute" (*continued*)	referral to liver transplant center (See acute ingestion section). Asymptomatic patient with *either* serum APAP concentration >10 mg/L (66 μmol/L) *or* serum AST/ALT ≥50 IU/L: NAC treatment same as "Acute;" recheck laboratory tests for APAP, AST/ALT at the end of 12 h of NAC treatment; if serum APAP <10 mg/L (66 μmol/L) *and* serum AST/ALT <50 IU/L, terminate NAC treatment; otherwise, continue NAC treatment until serum APAP <10 mg/L (66 μmol/L) *and* serum AST/ALT <50 IU/L. Asymptomatic patient with serum APAP concentration <10 mg/L (66 μmol/L) *and* AST/ALT <50 IU/L: No further treatment for APAP overdose is needed.		

Alcohol

Ethylene glycol (EG)

- Neurologic: CNS dysfunction/depression, coma; multiple cranial nerve deficits.
- Metabolic: Anion gap metabolic acidosis.
- CV: Cardiopulmonary failure.
- GU: Renal failure.

Serum bicarbonate <20 mmol/L or arterial pH <7.30: IV sodium bicarbonate 1–2 mmol/kg boluses, target blood pH 7.40, and urine pH 7.0–8.0.

Known or high index of suspicion of ingestion, clinical poisoning, or serum EG level ≥20 mg/dL (3.2 mmol/L):

- IV 4MP 15 mg/kg followed by 10 mg/kg every 12 h × 4 doses, and then 15 mg/kg every 12 h thereafter until toxic alcohol is undetectable and clear clinical–biochemical recovery; all infusions over 30 min.

OR

- IV ethanol (10% solution in D5W) 10 mL/kg over 1 h followed by 1.5 mL/kg/h, target serum ethanol 100 mg/dL until toxic alcohol is undetectable and clear clinical–biochemical recovery.

Maximize GFR: IV NS target urine output 2–4 mL/kg/h.

IV Pyridoxine 3–5 mg/kg/d *or* 50 mg every 6 h until toxic alcohol is undetectable and acidemia resolved.

IV thiamine 100 mg/d *or* every 6 h until toxic alcohol is undetectable and acidemia resolved.

Consider hemodialysis when serum EG ≥25 mg/dL (4.0 mmol/L) and acidemia or renal insufficiency.

- 4MP dosing: Administer the next scheduled dose if ≥6 h since last dose; during hemodialysis, dosing is every 4 h; end of dialysis and time of last dose 1–3 h administer half of next scheduled dose; >3 h administer next scheduled dose.
- Ethanol therapy: Increase to 3.0 mL/kg/h at the time of hemodialysis and decrease to 1.5 mL/kg/h after hemodialysis;

Clinical–biochemical manifestation: Latent onset 8–12 h; variable with coingestion of ethanol.

Osmol and anion gap: An inverse relationship occurs with time; not a sensitive surrogate marker for toxic alcohol exposure.

Sodium bicarbonate: Large doses may be needed to treat metabolic acidosis; hypocalcemia.

4MP and ethanol only *inhibit* metabolism of toxic alcohols.

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
• Ethylene glycol (EG) (*continued*)		closely monitor serum ethanol and glucose level; adverse events include hypoglycemia, fluid overload, inebriation. • Continue 4MP/ethanol treatment until undetectable serum EG level (significant EG may rebound following hemodialysis).	
Isopropanol • Neurologic: CNS dysfunction/depression, coma. • Metabolic: Acetonemia, acetonuria, anion gap metabolic acidosis (mild). • CV: Hypotension, myocardial depression.	Supportive care	Maximize GFR: See Ethylene glycol. Hemodialysis consideration: Hypotension (systolic <100 mm Hg), coma, or serum isopropanol ≥400 mg/dL (66.7 mmol/L).	Isopropanol is metabolized to acetone, and high serum acetone concentration can give falsely high serum Cr concentration with Jaffe-alkaline-picrate-colorimetric method used on automated chemistry instruments.
Methanol (MeOH) • Neurologic: CNS dysfunction/depression, coma. • Metabolic: Anion gap metabolic acidosis. • Ophthalmologic: Blindness.	Serum bicarbonate <20 mmol/L or arterial pH <7.30: See Ethylene glycol. Known or high index of suspicion of ingestion, clinical poisoning, or serum MeOH level exceeding	Maximize GFR: See Ethylene glycol. IV leucovorin 2 mg/kg (infusion rate <160 mg/min) every 4–6 h until toxic alcohol is undetectable; clear clinical–biochemical recovery; if leucovorin not available IV folic acid	Clinical–biochemical manifestation, osmol and anion gap, sodium bicarbonate, 4MP/ethanol: See Ethylene glycol.

	20 mg/dL (6.3 mmol/L): IV 4MP *or* ethanol; See Ethylene glycol.	50–70 mg every 4 h; leucovorin preferred over folic acid. Consider hemodialysis when CNS, visual, or funduscopic abnormality; serum MeOH ≥25 mg/dL (7.8 mmol/L); acidemia or renal insufficiency. • Leucovorin: Administer additional dose at end of hemodialysis. • Continue 4MP/ethanol treatment until undetectable serum MeOH level (significant MeOH may rebound following hemodialysis).	
Anticholinergics (e.g., antihistamines [H_1-blockers], cyclic antidepressants, antispasmodics, antipsychotics, antiparkinsonian drugs, mydriatics, chlorpheniramine, cyclizine, cyproheptadine, diphenhydramine, hydroxyzine, meclizine, promethazine, tripelennamine, scopolamine, ipratropium, cyclobenzaprine, plants: *Myristica fragrans*	Hallucinations, agitated delirium: See Withdrawal syndrome, sedative hypnotics; IV diazepam or lorazepam, propofol or pentobarbital. Physostigmine diagnostic aid: Selective use in anticholinergic agitation and delirium resulting from unknown ingestion; a positive response (e.g., patient awakens, provides history	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients followed by activated charcoal (oral/nasogastric) 1–2 g/kg.	Physostigmine: Contraindications include bronchospasm, mechanical intestinal or urogenital tract obstruction, early (<6 h) cyclic antidepressant overdose, overdose with cardiac

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
[nutmeg], *Brugmansia, Datura, Hyoscyamus niger, Solanum, Amanita muscaria*) • Ophthalmologic: Mydriasis (variable). • CV: Hypertension, tachycardia. • Skin: Warm, dry, flushed; dry mucous membranes. • GI: Decreased bowel sounds; ileus. • GU: Urinary retention. • Neurologic: Loss of short-term memory, confusion, disorientation, visual/auditory hallucinations, ataxia/incoordination, picking/grasping movements, extrapyramidal reactions, psychosis, coma, agitated delirium, respiratory failure, hyperthermia, seizures.	consistent with anticholinergic toxicity) obviates additional testing (e.g., cranial CT and lumbar puncture); IV physostigmine 0.5–2 mg at ≤0.5 mg/min (Peds: 0.02 mg/kg at 0.5 mg/min), if no reversal of anticholinergic effect within 10–20 min, administer an additional 1–2 mg. Hyperthermia: Rapid cooling measures. Urinary retention: Insert Foley catheter.		conduction delay, and cyclic antidepressant poisoning with high-dose/drug-level phenomena (e.g., hypotension, coma, seizures, cardiac conduction delays, and dysrhythmias); complications include dehydration and rhabdomyolysis.
Anticonvulsants Carbamazepine (CBZ) • Neurologic: Slurred speech; nystagmus; lethargy; ataxia;		GI decontamination consideration (after patient stabilized and precautionary measures to	Pharmacobezoar: Serum CBZ concentration continues to significantly rise or not significantly

ophthalmoplegia, diplopia; depressed sensorium, coma; absent doll's eye/caloric reflexes; respiratory depression; cyclic coma; seizures; SIADH. • CV: Atrial and ventricular dysrhythmias; intraventricular conduction defects (e.g., prolonged QRS/QTc); heart blocks. • Anticholinergic syndrome: Hyperthermia, sinus tachycardia, hypertension, urinary retention, mydriasis, ileus. • Adventitious movements: Oculogyric crisis, dystonia, opisthotonos, choreoathetosis, ballismus.	minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients; activated charcoal (oral/nasogastric) 1–2 g/kg followed by activated charcoal hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h, not in patients with decreased bowel sounds/ileus; WBI (See Box 96-2) for large ingestion of modified release formulation; procedural removal of bezoar/concretion. Extracorporeal elimination (i.e., hemodialysis, hemoperfusion, CVVH) consideration: Persistently high serum CBZ concentrations and coma.	decreasing over time, delayed symptoms, relapse, or deterioration as late as 48 h after overdose; imaging studies with contrast to confirm diagnosis. Risk stratification based on *peak* serum CBZ concentration: • Delayed peak concentration following modified released formulation may be >96 h. • >40 mg/L (170 μmol/L) increased risk for coma, seizures, respiratory failure, cardiac conduction defects.
Phenytoin • Neurologic: Nystagmus; blurred vision, diplopia; slurred speech; ataxia; tremor; drowsiness, lethargy; confusion; hallucinations; psychosis; seizures;	Activated charcoal (oral/nasogastric) 1–2 g/kg; administer additional activated charcoal hourly, every 2 h, or every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h in patients with serum phenytoin	

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
progressive CNS depression, coma; respiratory depression. • CV: Dysrhythmias; hypotension; heart failure; respiratory arrest; asystole from *propylene glycol* toxicity during rapid IV phenytoin administration (e.g., >50 mg/min).		concentration >40 μg/mL, moderate neurologic toxicity, or rising serum phenytoin levels following initial activated charcoal dose, but not in patients with decreased bowel sounds/ileus; discontinue before drug levels reach therapeutic range in patients on phenytoin therapy.	
Valproic acid (VPA) • Neurologic: Drowsiness, lethargy; confusion, disorientation; seizures; encephalopathy; cerebral edema; obtundation, coma; respiratory failure. • CV: Tachycardia; hypotension. • GI: Pancreatitis; hepatotoxicity. • Metabolic: Anion gap metabolic acidosis; hyperammonemia; hypernatremia; hypocalcemia.	Coma, symptomatic hyperammonemia, symptomatic hepatotoxicity, or rising serum ammonia levels: IV L-carnitine 100 mg/kg (max 6 g) over 30 min followed by 15 mg/kg every 4 h over 10–30 min until clinical improvement; consider treatment for patients with serum VPA >450 μg/mL. Acute VPA overdose without hepatic enzyme abnormalities or hyperammonemia: Consider oral	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients followed by activated charcoal (oral/nasogastric) 1–2 g/kg; WBI (See Box 96-2) for large ingestion of modified release formulation; procedural removal of bezoar/concretion. Consider hemodialysis when coma, hemodynamic instability,	Risk stratification based on *peak* serum VPA concentration: • Delayed peak concentration may be >10 h postingestion. • >450 μg/mL moderate-to-major outcome. • >850 μg/mL hypotension, coma, respiratory depression, aspiration, metabolic acidosis. Hemodialysis and CAVH/CVVH are not equivalent, and they are

• Hematologic: Thrombocytopenia; leukopenia.	L-carnitine 100 mg/kg/d (max 3 g) divided every 6 h.	rapid deterioration, hepatic dysfunction, metabolic acidosis unresponsive to fluids, serum VPA >1,000 μg/mL; terminate when serum VPA is in the therapeutic range.	not mutually exclusive; CAVH/CVVH may be the only option in hypotensive patients until hemodialysis can be tolerated.
Antidepressant Cyclic antidepressant • Neurologic: CNS depression; seizures; coma. • CV: Tachycardia; hypotension; ventricular dysrhythmias.	ECG (maximal limb-lead) QRS ≥120 ms or RaVR ≥3 mm or R/SaVR ≥0.7: IV sodium bicarbonate 1–2 mmol/kg bolus × 2; repeat ECG every 3–5 min; IV sodium bicarbonate 1–2 mmol/kg bolus until the QRS duration stabilized. Seizures and dysrhythmias: Current ACLS toxicology guidelines and avoid class IA/IC antidysrhythmics; class IB may be useful.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients, followed by activated charcoal (oral/nasogastric) 1–2 g/kg; WBI (See Box 96-2) for large ingestion of modified release formulation; procedural removal of bezoar/concretion.	Bupropion seizures: Therapeutic or overdose; brief; latent onset 10–24 h (sustained-release preparations). Amoxapine seizures: Recurrent and prolonged.
Monoamine oxidase inhibitors (MAOI) • Latent-onset toxicity (6–24 h); sympathetic hyperactivity with CNS excitation and peripheral sympathetic	Sympathetic hyperactivity: IV BZD; neuromuscular paralysis and intubation; cooling measures. Severe hypertension and tachycardia: IV nitroprusside and esmolol.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See Cyclic antidepressant.	MAOI: Combined with serotoninergic drugs is a significant risk for severe serotonin syndrome/death; interaction with sympathomimetics (e.g., amphetamines, ephedrine,

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
stimulation (e.g., hypertension, tachycardia, tachypnea, pyrexia, agitation, confusion, tremor, hyperreflexia); may progress to CNS depression and CV collapse.	Hypotension: IV norepinephrine or epinephrine (avoid dopamine).	Maximize GFR: IV NS target urine output 2–4 mL/kg/h.	phenylephrine) and tyramine in food (e.g., aged cheese, smoked/pickled meats, red wine, pasteurized light, pale beers) precipitate "hypertensive crisis" (i.e., agitation, tachycardia, hyperthermia, seizures) and ICH.
(Selective) serotonin reuptake inhibitor (SSRI) • Neuroexcitation: Neuromuscular hyperactivity (e.g., tremor, clonus, myoclonus, hyperreflexia, hypertonia/pyramidal rigidity); altered mental status (e.g., agitation, excitement, confusion); autonomic hyperactivity (e.g., diaphoresis, fever, mydriasis, tachycardia, tachypnea). • Serotonin syndrome (toxicity): Spontaneous clonus;	Neuroexcitation/serotonin syndrome: IV BZD; IV chlorpromazine 50 mg, repeat in 2–3 h as needed or oral (gastric tube) cyproheptadine 4–8 mg (max 24 mg/d), and repeat every 2 h if no improvement or recurrent signs; neuromuscular paralysis and intubation; cooling measures.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See Cyclic antidepressant. Maximize GFR: See MAOI.	Serotonin syndrome (toxicity): Can be caused by all antidepressants, alone or in combination, in therapeutic or overdoses, in combination with other serotonergic agents; escalating dose or additional serotonergic agent during chronic therapy; a spectrum of serotonin-related adverse events progressing to toxicity; complications include rhabdomyolysis, dysrhythmias.

inducible clonus *and* agitation or diaphoresis; ocular clonus *and* agitation or diaphoresis; tremor *and* hyperreflexia; hypertonic *and* temperature >38°C; *and* ocular or inducible clonus.			Venlafaxine: Seizures; prolonged QRS/QTc; ventricular dysrhythmias. Citalopram/escitalopram: Seizures; prolonged QTc; wide-complex tachycardia. Cyproheptadine: Urinary retention.
Antimalarial Chloroquine • CV: Hypotension; intraventricular conduction defects (e.g., prolonged QRS/QTc); heart block; ventricular dysrhythmias. • Neurologic: CNS depression; dizziness, headache; seizures. • Metabolic: Hypokalemia. • Respiratory: Respiratory depression; pulmonary edema.	Symptomatic/severe poisoning or known/suspected chloroquine ingestion >5 g: • Rapid orotracheal intubation and *avoid* thiopental induction. AND • IV epinephrine 0.25 μg/kg/min followed by increments of 0.25 μg/kg/min until systolic arterial pressure ≥100 mm Hg). AND • IV diazepam 2 mg/kg over 30 min followed by 1–2 mg/kg/d × 2–4 d. • Transient CV compromise requires additional epinephrine and other catecholamines.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients followed by activated charcoal (oral/nasogastric) 1–2 g/kg.	Acute chloroquine poisoning results in hypokalemia (intracellular shifts, not total body depletion) that reflects severity of toxicity; carefully monitor serum potassium concentrations, particularly among patients who also receive catecholamine infusions; overzealous potassium replacement invokes risk of subsequent hyperkalemia.

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
Chloroquine (*continued*)	Heart block or ECG (maximal limb-lead) QRS ≥120 ms: IV sodium bicarbonate 1–2 mmol/kg bolus × 2; repeat ECG every 3–5 min; IV sodium bicarbonate 1–2 mmol/kg bolus until QRS duration stabilized. Seizures and dysrhythmias: Current ACLS toxicology guidelines and avoid class IA/IC/III antidysrhythmics; class IB may be useful.		
Quinine • Ophthalmologic: Blurred vision; visual field constriction, scotomata; diplopia; altered color perception; complete blindness (sudden visual loss can occur ≥14 h after overdose); pupils dilated and unreactive in proportion to the degree of visual impairment.	Heart block or ECG (maximal limb-lead) QRS ≥120 ms (See Chloroquine). Seizures and dysrhythmias: See Chloroquine. Hypoglycemia: IV dextrose (monitor serum potassium and QTc) *or* IV octreotide 50 µg/h *or* IM octreotide 100 µg.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients; activated charcoal (oral/nasogastric) 1–2 g/kg followed by hourly, every 2 h, or every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not	Complete blindness reported only after oral quinine ingestion and expected (can be lower) when serum quinine >20 mg/mL in the first 10 h following ingestion; residual impairment (e.g., peripheral field defects, scotomata, impaired color vision, complete blindness) in severe cases.

• CV: Hypotension; intraventricular conduction defects (e.g., prolonged QRS); complete heart block; dysrhythmias (e.g., torsades de pointes, ventricular tachycardia, ventricular fibrillation). • Neurologic: Delirium, coma, and seizures; tinnitus, deafness. • Metabolic: Hypoglycemia rare except during high-dose IV quinine and concomitant metabolic stresses (e.g., malaria, malnutrition, alcoholism). • Respiratory: ARDS.		in patients with decreased bowel sounds/ileus.	Patients on therapeutic doses of quinine may experience nausea, vomiting, decreased hearing acuity, tinnitus, headache, and tachycardia ("cinchonism").
Beta-adrenergic blocker (BB) • CV: Hypotension and bradycardia (pindolol-tachycardia and hypertension); heart failure, pulmonary edema; IVCD (e.g., acebutolol, betaxolol, carvedilol, metoprolol, oxprenolol, and propranolol); heart block; ventricular dysrhythmias; asystole.	Bradycardia: • IV atropine (max 3 mg). • IV glucagon 50–150 mg/kg and start infusion dose to give effective bolus dose each hour (e.g., heart rate increased after two successive 5-mg boluses, then administer 10 mg/h). • Cardiac pacing: Optimal pacing rate 50–60 beats per minute.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients followed by activated charcoal (oral/nasogastric) 1–2 g/kg; WBI (See Box 96-1) for large ingestion of modified release formulation; endoscopic removal of bezoar/concretion.	Bradycardia/hypotension seldom responds to atropine and fluid bolus. Glucagon most effective in increasing heart rate. Cardiac pacing: Often fails to capture; blood pressure not always restored. Catecholamine use/dosing based on cardiodynamic and

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• Neurologic: Depressed consciousness; confusion; lethargy; coma; seizures (especially BB with high lipid solubility–propranolol, pentbutolol, metoprolol). • Respiratory: Bronchospasm. • Metabolic: Hypoglycemia/ hyperglycemia (rare).	Hypotension: IV NS bolus, catecholamine(s). QRS >120 ms: IV sodium bicarbonate 1–2 mmol/kg bolus; repeat for recurrent QRS widening. Hypodynamic myocardium. Euglycemic clamp:IV regular insulin 1 IU/kg bolus followed by infusion 0.5 IU/kg/h titrated every 30 min to desired effect on contractility or blood pressure (echocardiography for measuring myocardial response); euglycemia = serum glucose 100–250 mg/dL (5.5–14 mmol/L) is maintained by IV dextrose 25 g bolus with initial insulin bolus (unless serum glucose >400 mg/dL [22 mmol/L]) followed by dextrose infusion 0.5 g/kg/h titrated based on bedside glucose monitoring every 20–30 min until serum glucose is stable and then every 1–2 h; replace potassium if <2.5 mmol/L *and* a source of potassium loss.	Hemodialysis consideration: BB with significant renal clearance (e.g., acebutolol, atenolol, bisoprolol, carteolol, pindolol, sotalol, nadolol). Extraordinary measures: Extracorporeal circulatory support, intra-aortic balloon pump counterpulsation, prolonged CPR (e.g., 2.5–4 h).	hemodynamic monitoring (e.g., norepinephrine for hypotension due to low SVR); no one catecholamine superior for CV drug toxicity and may require large doses of multiple adrenergic agents. Euglycemic clamping: Response not immediate and increase chance of benefit with early detection of hypodynamic myocardium and early initiation of therapy; numerical hypoglycemia, hypokalemia, hypophosphatemia, hypomagnesemia.

Body packer

- Asymptomatic: Presents in custody of law enforcement officer(s) requesting medical evaluation or retreival of contraband from the GI tract; *medicolegal* issues may be involved.
- Symptomatic: Typical signs/symptoms of the drug (e.g., cocaine, heroin) being concealed.
- May present with or develop signs/symptoms of intestinal obstruction, intestinal perforation, peritonitis.

Asymptomatic: Administer an oral dose of water-soluble contrast (e.g., Gastrografin) 1 mL/kg; perform abdominal radiographs (supine and upright) at least 5 h after contrast administration; perform daily abdominal radiographs if radiographs are positive and after a spontaneous bowel movement; check all bowel movements for drug packets; continue until after passage of two packet-free bowel movements and negative abdominal radiographs; oral intake ad lib.

Symptomatic *heroin* body packer: IV naloxone infusion (See Opioid); activated charcoal (oral/nasogastric) 1–2 g/kg, and WBI (See Box 96-2) after patient stablized, patient is able to tolerate charcoal/WBI, and precautionary measures to minimize aspiration.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Body packer (*continued*)	Surgical intervention: Symptomatic cocaine body packer; failed medical management in symtomatic heroin body packer; intestinal obstruction/perforation; packets fail to progress through the GI tract after conservative management. Consider endoscopic retrieval of retained packets in the stomach by an *experienced* endoscopist.		
Calcium channel antagonist (CCA) • CV: See Beta-adrenergic blocker (BB); bepridil-prolonged QTc and torsade de pointes. • Neurologic: See BB. • Metabolic: Hyperglycemia; lactic acidosis. • Respiratory: Noncardiogenic pulmonary edema. • Abdomen: Ileus; mesenteric ischemia/infarction.	Bradycardia: See BB. Hypotension: See BB. QRS >120 ms: See BB. Hypodynamic myocardium • See BB. • IV calcium gluconate (10%) 0.6 mL/kg bolus (0.2 mL/kg 10% calcium chloride) over 5–10 min followed by continuous calcium gluconate infusion	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See BB. Extraordinary measures: See BB.	See BB. Acidemia worsens myocardial dysfunction. Calcium treatment: Mixed clinical experience (disappointing at times), primarily inotropic effect; gluconate safest.

	at 0.6–1.5 mL/kg/h (0.2–0.5 mL/kg/h 10% calcium chloride); titrate infusion to affect improved blood pressure/contractility; follow ionized calcium levels every 30 min initially and then every 2 h maintaining ionized calcium twice normal.		
Cardioactive steroid (e.g., digoxin, digitoxin, oleander, and bufo toxin) Digoxin • General: Nausea, vomiting; fatigue. • CV: Variety of dysrhythmias; atrial tachycardia with variable atrioventricular (AV) block (paroxysmal atrial tachycardia 2:1 block), accelerated junctional rhythm (regularized atrial fibrillation), and fascicular tachycardia highly suggestive and bidirectional ventricular tachycardia (i.e., narrow-complex tachycardia with right bundle branch morphology) highly specific for digitalis toxicity.	Symptomatic patients, cardiac dysrhythmias that threaten or result in hemodynamic compromise, serum potassium >5.0 mmol/L, serum digoxin concentration >10.0 ng/mL (12.8 nmol/L) 6 h after overdose or >15 ng/mL (19.2 nmol/L) at any time: IV digoxin-specific antibody fragments (e.g., Digibind® or DigiFab®): • From dose ingested: One vial (40 mg) binds 0.6 mg of digoxin; for example: Ingestion of 3 mg of digoxin (bioavailability 80% [0.8]) requires four vials. • From serum digoxin concentration, See Box 96-3.	GI decontamination considerations (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal (oral/nasogastric) 1–2 g/kg followed by hourly, every 2 h, or every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus.	Chronic digoxin toxicity: Similar to acute toxicity and hallucinations, visual disturbances such as cloudy or blurred vision, loss of vision, and yellow-green halos or everything appearing washed in yellow (xanthopsia); normo- or hypokalemia is more common in patients with heart disease. Predisposition to toxicity: Hypokalemia, hypomagnesemia, and hypercalcemia, renal dysfunction. Serum digoxin levels most reliably correlate with toxicity when obtained ≥6 h after digoxin administration.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• CNS: Headache; weakness; dizziness; confusion; syncope; coma.	• By titration: Administer four to six vials and repeat depending on clinical effect. If *digoxin-specific antibody fragments unavailable*, temporary transvenous cardiac pacing; IV magnesium sulfate 2.5 g (10 mmol) over 5 min for ventricular tachydysrhythmias, repeat as needed. Acute allergic reaction to digoxin-specific antibody fragments: Stop infusion; treat according to current guidelines.		Naturally occurring cardioactive steroids from plants and animals can cross-react with the digoxin assay; degree of cross-reactivity is unknown and no good correlation between serum levels and toxicity. A false-positive digoxin assay (<3 ng/mL) may occur in patients (e.g., neonates, patients with renal insufficiency, liver disease, and pregnancy) not receiving digoxin therapy. Dysrhythmias: IV magnesium worsens AV block in bradydysrhythmias; avoid class IA antidysrhythmics drugs. DigiFab (1,200 mg) are safe and effective treatment for yellow oleander–induced cardiac dysrhythmias (e.g., bradycardia (<40/min), sinus arrest or block, atrial tachydysrhythmias, second- or third-degree AV block.

Envenomation Elapidae (coral snakes) • Local effects: Little or no pain or swelling at the bite site; paresthesias radiating proximally; muscle fasciculations. • Systemic effects: Latent onset (hours); drowsiness or euphoria; nausea, vomiting, increased salivation; bulbar-type paralysis and progresses to peripheral paralysis; extraocular muscle paresis, ptosis, pinpoint pupils, dysphagia, dysphonia, slurred speech, and laryngeal spasm; respiratory failure; CV collapse.	Impending respiratory failure (e.g., any sign of cranial nerve palsy/paralysis, trismus, laryngeal/pharyngeal spasm, cyanosis): Prophylactic endotracheal intubation and mechanical ventilation. Clinical envenoming or strong clinical suspicion for or proven coral snake bite: IV coral snake antivenom 4–6 vials (adults and Peds) with each vial diluted in 50–100 mL of NS and administered over 1 h; if signs/symptoms appear or progress, administer 4–6 more vials of antivenom. Allergic reaction to antivenom: Stop infusion; treat according to current guidelines. Bite site: Local wound care; antibiotics for infected wounds; tetanus prophylaxis.	Envenomation is a *dynamic* process. Venoms do not appear to cross the blood–brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, or intracranial bleeding. Precaution: Be prepared to manage acute anaphylactic (shock) and anaphylactoid reactions prior to administering antivenom. Antivenom: Equine origin; may be effective in late presenters. Serum sickness: May occur 7–21 d following antivenom therapy; treat with oral steroids, antihistamines, and NSAIDs.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Viperidae (subfamily Crotalinae: pit vipers, e.g., rattle snake) • Local effects: Swelling, tenderness, tenseness, hypesthesia, pain; muscle necrosis; compartment syndrome; ecchymosis; bloody effluent from wound; lymphangitis; regional adenopathy; hemorrhagic bullae or serum-filled vesicles at bite site and along bitten extremity; petechiae or purpura. • Systemic effects: Nausea, vomiting; weakness; diaphoresis; fever; chills; dizziness; syncope; minty, rubbery, or metallic taste in mouth; muscle fasciculations; paresthesias of scalp, face, digits; systemic bleeding at any anatomic site; hypotension; noncardiogenic pulmonary edema; renal failure;	*Progression* of venom effects (i.e., worsening of local injury [e.g., pain, swelling, and ecchymosis], coagulopathy, *or* systemic effects [e.g., hypotension and altered mental status]): IV CroFab® • Administer 4–6 vials (adults or Peds); closely monitor for further progression of local effects and systemic symptoms, and laboratory studies [i.e., complete blood count (CBC), PT/INR, fibrin, fibrin degradation products] are repeated 1 h after completing antivenom infusion; administer additional rounds of antivenom (4–6 vials) if initial control (i.e., reversal or marked attenuation of all venom effects) has not been achieved; continue this pattern until control is evident; then administer two vials of CroFab every 6 h for three additional		Envenomation is a *dynamic* process. Venoms do not appear to cross the blood–brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, or intracranial bleeding. Precaution: See Elapidae. Antivenom: Ovine origin; most effective within first 24 h following envenomation; may be beneficial in late presenters with severe findings (e.g., coagulopathy); limited efficacy in preventing wound necrosis or reversing cellular damage; thrombocytopenia may be resistant to antivenom therapy. Serum sickness: See Elapidae.

neuromuscular respiratory failure may occur following severe Mojave envenomation. • Hematologic effects: Systemic coagulopathy	doses; most cases, 8–12 vials to establish initial control. • Reconstituted each CroFab vial with NS 10 mL and roll vials between hands; dilute total dose to be administered in NS 250 mL and infused over 1 h. Acute allergic reaction to antivenom: See Elapidae. Suspected compartment syndrome: Measure intracompartmental pressures using any standard device; if pressures >30–40 mm Hg, elevate limb, and administer additional 4–6 vials of antivenom over 1 h; if this fails to reduce compartment pressure within 4 h and evidence of circulatory compromise, fasciotomy may be required. Bite site: See Elapidae. Hemorrhagic blebs: Unroof after the first few days; further debridement if significant necrosis (after coagulopathy has resolved).	

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Brown spider (*Loxosceles* sp., e.g., brown recluse) • Local effects: Dermonecrosis. • Systemic (viscerocutaneous) effects: Uncommon; latent onset 24–72 h after the bite and occasionally occur before cutaneous findings become impressive; flu-like symptoms with fever, chills, headache, malaise, weakness, nausea, vomiting, myalgias, and arthralgias; hemolytic anemia with hemoglobinemia; hemoglobinuria; jaundice; thrombocytopenia; disseminated intravascular coagulation; shock; seizures; coma; secondary acute renal failure; not necessarily correlate with cutaneous severity; rapidly progressive and severe particularly in children.	Supportive care.		No proven therapeutic treatment for local or systemic effects.

Widow spider (*Latrodectus* sp., e.g., black widow) • Local effects: Bite site may be visible, area slightly warm, diaphoresis, and blanched with a surrounding erythematous, indurated zone; minimal swelling. • Systemic effects: Gradual progression; fever, headache, diaphoresis, nausea, vomiting, restlessness, anxiety; tachycardia and hypertension; pain, dull ache spreading to local muscle groups and then to regional muscle groups, muscles spasm with resultant rigidity.	Symptomatic treatment: IV BZD and opioid. Severe clinical envenoming, inadequate response to BZD and opioid, CV comorbidities, pregnant patient, or patient in labor: IV antivenom (preferable) one reconstituted vial further diluted in 50–100 mL of NS over 30 min *or* IM one reconstituted vial in the anterolateral thigh signs/symptoms should completely resolve within a few hours; administer second vial if clinically indicated. Acute allergic reaction to antivenom: See Elapidae.	Envenomation is a *dynamic* process. Venom does not appear to cross the blood–brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, or intracranial bleeding. Precaution: See Elapidae. Antivenom: Equine origin; most effective in the acute setting; may be beneficial in late presenters (e.g., 96 h) with prolonged symptoms. Serum sickness: See Elapidae.
Scorpion (*Centruroides* sp.) • Local effects: Intense pain exacerbated by light palpation or tapping over the site. • Systemic effects: Restlessness, anxiety, hypersalivation, dysphagia, difficulty focusing or temporary blindness, roving	Symptomatic treatment: IV BZD and judicious opioid use; consider beta-adrenergic blocker for hemodynamically significant tachycardia. Clinically significant signs of scorpion envenomating (e.g., loss of muscle control, roving	Envenomation is a *dynamic* process. Venoms do not appear to cross the blood–brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, or intracranial bleeding.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
eye movements, tachypnea, respiratory distress, wheezing, stridor, hypertension, tachycardia, involuntary voiding of stool/urine, muscle fasciculations/spasm, alternating opisthotonus and emprosthotonus, and paralysis; extreme neuromuscular hyperactivity.	or abnormal eye movements, slurred speech, respiratory distress, excessive salivation, frothing at the mouth, and vomiting), inadequate response to BZD and opioid: IV Anascorp®. • Administer 3 vials (adults or Peds); closely monitor for resolution of clinically important signs of envenomating during and up to 60 min following antivenom infusion; administer additional doses of antivenom if needed one vial at a time at 30–60-min intervals and monitor for resolution of clinically important signs of envenomating during and up to 60 min following antivenom infusion. • Reconstitute each Anascorp® vial with NS 5 mL and mix by continuous gentle swirling; dilute		Precaution: See Elapidae. Antivenom: Equine origin. Serum sickness: See Elapidae.

	total dose to be administered in NS 50 mL, and infuse over 10 min. Acute allergic reaction to antivenom: See Elapidae.		
Herbicide Chlorate salts • GI: Vomiting, diarrhea; abdominal pain. • Hematologic: Methemoglobinemia (cyanosis); hemolytic anemia (hyperkalemia); Heinz bodies; ghost cells. • GU: Hemoglobinuria (black-brown urine); acute renal failure.	Symptomatic methemoglobinemia or methemoglobin >20%: • Ventilate and oxygenate with 100% oxygen. • IV methylene blue 1–2 mg/kg over 5 min, repeat doses may be needed; onset of action ≤30 min; efficacy may be limited (chlorate inactivates glucose-6-phosphate dehydrogenase) and may need to proceed with hemodialysis.	Prolonged action of chlorate on red blood cells suggests that early hemodialysis should be considered.	Repetitive or continuous methylene blue dosing and GI decontamination may be needed when there is continued absorption or slow elimination of an agent producing methemoglobinemia: IV methylene blue 0.05% (in NS) 0.1 mg/kg/h *or* 3–7 mg/h has been suggested.
Chlorophenoxy herbicides (e.g., 2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T], and 2-methyl-4-chlorophenoxypropionic acid [MCPP])	Symptomatic patients: Urine alkalinization with IV sodium bicarbonate 2 mmol/kg bolus followed by continuous infusion of sodium bicarbonate 150 mmol mixed in 1,000 mL D5W starting at 1.5–2.0 times the maintenance	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal (oral/nasogastric) 1–2 g/kg.	No published reports of acute chlorophenoxy herbicide poisoning following dermal or inhalational exposure in at least the last 20 years, and no reported fatalities from such exposures in the history of chlorophenoxy herbicide use.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• GI: Oral burning, vomiting, abdominal pain, diarrhea, GI hemorrhage. • CV: Hypotension, intraventricular conduction defects, supraventricular and ventricular dysrhythmias, bradycardia. • Respiratory: Tachypnea, respiratory insufficiency, pulmonary edema, hemoptysis. • Neurologic: Pyrexia; miosis, nystagmus; twitching or fasciculations, weakness, myotonia (may progress to rhabdomyolysis); hypertonia, hyperreflexia, or clonus; ataxia; agitation; confusion; hallucinations; CNS depression; seizures; coma. • GU: Renal failure. • Metabolic: Metabolic acidosis; hypocalcemia; hypokalemia.	rate, tirate to maintain urinary pH 8.0 and arterial pH <7.55; reassess clinical status/laboratory parameters (e.g., electrolytes, acid–base, urine pH) hourly; terminate when clear clinical–biochemical recovery.	Consider hemodialysis in the setting of severe poisoning; produces good herbicide clearance without need for urine pH manipulation and administration of substantial IV fluids.	

Diquat • Local caustic effects; similar to paraquat. • Respiratory: Bronchopneumonia; ARDS/acute lung injury; respiratory failure. • CV: Hypovolemia, shock; ventricular dysrhythmias, subendocardial hemorrhages, cardiac arrest. • GI: Nausea, vomiting, diarrhea, abdominal pains; ileus, abdominal distention, and rapid fluid sequestration in the GI tract; liver injury. • GU: Proteinuria; renal failure. • CNS: Seizures; pontine hemorrhages/infarction; brain stem infarction; coma. • Hematologic: Pancytopenia.	Management of diquat exposure similar to paraquat, and does not include investigational management strategy.		Systemic toxicity usually associated with ingestion and total amount of diquat cation ingested more important than its concentration in solution; systemic effects may be delayed up to 48 h following ingestion; mortality within hours to days following massive ingestion. Diquat may interfere with the Jaffé reaction for Cr measurement. Poor prognosis: Rapid onset of acute renal failure, intestinal ileus and subsequent fluid sequestration, ventricular dysrhythmias, pulmonary complications requiring ventilation, and coma. Pulmonary fibrosis is not been reported following diquat poisoning.
Paraquat • Local caustic effects. • GI: Painful ulceration of the lips, tongue, pharynx, and larynx (caustic injuries) leading	Optimal fluid resuscitation should be guided by central venous or pulmonary capillary wedge pressures.	Supplemental oxygen is withheld until the arterial oxygen tension <50 mm Hg and/or patient expresses respiratory distress.	Spontaneous vomiting is a near certainty following significant paraquat ingestions (e.g., irritant effects and emetic added to many formulations).

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
to dysphagia, cough, dysphonia, inability to clear secretions, esophageal perforation; vomiting; abdominal pain; hematemesis; diarrhea; pancreatitis; centrilobular hepatic necrosis; cholestasis. • CV: Hypovolemia; shock; dysrhythmias. • Respiratory: Cough; prominent pharyngeal membranes (pseudodiphtheria); mediastinitis; pneumothorax; hemoptysis; (hemorrhagic) pulmonary edema; progressive pulmonary fibrosis. • GU: Acute renal failure. • Neurologic: Coma, convulsions, cerebral edema. • Dermatologic: Caustic injury to skin, nails, cornea, conjunctiva, nasal mucosa. • Endocrine: Adrenal insufficiency.	Caustic injury to oral/GI tract: Current guidelines. Investigational management strategy: Patients presenting within 24 h of paraquat ingestion and have an expected mortality rate 50%–90% on nomogram (Fig. 96-2): IV cyclophosphamide 15 mg/kg in 200 mL of 5% glucose saline infused over 2 h × 2 d *and* IV methylprednisolone 1 g in 200 mL of 5% glucose saline infused over 2 h × 3 d, IV dexamethasone 5 mg every 6 h until $PaO_2 \geq 80$ mm Hg (11.5 kPa); if $PaO_2 < 60$ mm Hg (8.64 kPa), administer IV methylprednisolone 1 g in 200 mL of 5% glucose saline over 2 h × 3 d; if white blood cell counts <3,000/m^3 and initial cyclophosphamide therapy >2 wk, administer IV cyclophosphamide 15 mg/kg over 2 h × 1 d	GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): Oral/nasogastric activated charcoal 1–2 g/kg *or* fuller's earth (15% [w/L] aqueous suspension) 1–2 g/kg *or* bentonite (7% [w/v] aqueous slurry) 1–2 g/kg with a cathartic (e.g., magnesium salt or sorbitol 70%); IV antiemetic (e.g., ondansetron 8 mg; Peds: 0.2 mg/kg, max 8 mg) may be needed. Charcoal hemoperfusion: Initiate within 4 h of ingestion and continued for 6–8 h; CAVH reduces rebound in serum paraquat concentrations after hemoperfusion; hemodialysis may result in greater than or equal to renal paraquat clearance and should be performed for usual indications in acute renal	Serum and urine specimens should be placed in plastic containers and sent for qualitative and quantitative paraquat concentration determination; treatment of patient should continue until results are available. Serum paraquat concentrations measured within 28 h after ingestion have some prognostic value based on an empirically derived nomogram from clinical (*not* statistical) data (Fig. 96-1): Mortality rate 100% when initial serum paraquat >3 mg/L; cardiogenic shock and death with in 24 h of ingestion when serum paraquat >10 µg/mL. Paraquat may interfere with the Jaffé reaction for Cr measurement.

	(IV dexamethasone 5 mg every 6 h is continued until death or PaO_2 ≥80 mm Hg (11.5 kPa) and then gradually reduce dose).	failure or when hemoperfusion not available.
Hydrofluoric acid (HF) • Dermal exposure: At risk for systemic fluoride toxicity (See Oral exposure) >5% BSA *or* >1% BSA exposure to a product ≥50% HF.	Rapid irrigation with water ≥15 min; apply a 2.3%–2.5% calcium gluconate preparation in a water-soluble gel to exposed area(s) ≥30 min or until symptoms resolve. Pain unrelieved by gel therapy: • Regional intra-arterial: Place catheter in direction of blood flow by Seldinger technique; continuously monitor arterial waveform (arteriography if any concern as to adequate placement); infuse 50 mL of 2.5% calcium gluconate in NS over 4 h; repeated doses may be required over 12–24 h. OR • Administer 40 mL of a 2.5% calcium gluconate solution by Bier block technique (i.e., catheterize a distal vein and exsangui-	Wound management for acid burns.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• Dermal exposure: (*continued*)	nate extremity by elevation and compression with an Esmarch bandage; inflate blood pressure cuff to 100 mm Hg above systolic pressure; and maintain for 15–20 min following calcium administration; gradually deflate cuff over 5 min).		
• Inhalation exposure: Airway and pulmonary injury, respiratory failure; at risk for systemic fluoride toxicity (See Oral exposure); poisoning; progression of minimal symptoms over time.	Respiratory support; nebulized 25% calcium gluconate may improve symptoms following mild exposure.		
• Oral exposure: Risk of systemic fluoride toxicity in deliberate or accidental ingestion of products >7% HF; minimally symptomatic patients may rapidly progress to CV collapse.	Oral calcium- or magnesium-containing antacids 30–60 mL. History suggestive of a substantive exposure that may lead to systemic toxicity: • IV calcium chloride 1 g over 30 min; patients with normal		Resuscitation from cardiac arrest following systemic fluoride toxicity is rare; focus on *early* intervention to prevent cardiac dysrhythmias and arrest.

	vital signs and remain stable should be monitored with serum calcium levels every 30 min for the first 2–3 h; IV calcium chloride 1 g boluses to maintain serum calcium concentration in the high normal laboratory reference range; repeat as needed; a fall in serum calcium concentration below the normal range, dysrhythmias, or a fall in blood pressure is treated with IV calcium chloride 2–3 g boluses every 15 min. OR • IV magnesium sulfate 2–6 g over 30 min followed by an infusion 1–4 g/h; additional magnesium boluses as indicated by careful clinical assessments and laboratory investigations.		All patients should be admitted to an ICU following a deliberate HF ingestion.
Isoniazid (INH) • Dizziness, slurred speech, blurred vision, and visual hallucinations (e.g., bright colors, spots, strange designs); stupor and coma can rapidly develop, followed by intractable tonic–clonic	First sign of neurotoxicity: IV diazepam or equivalent *and* pyridoxine in milligram doses equal to the amount of INH ingested or 5 g in cases of unknown amount of ingestion administered over 30–60 min.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) for acutely ill patients followed by activated charcoal	

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
generalized or localized seizures, hyperreflexia, or areflexia; CV and respiratory collapse. • Metabolic: Severe metabolic acidosis, hyperglycemia, ketonuria, and hyperkalemia. • Triad: Metabolic acidosis refractory to sodium bicarbonate therapy, seizures refractory to anticonvulsants and coma.	Seizing patients: IV diazepam or equivalent *and* pyridoxine (milligram doses equal to the amount of INH ingested or 5 g in cases of unknown amount of ingestion) at 500 mg/min until seizures terminate and remainder of dose infused over next few hours; repeat pyridoxine dose if seizures persist or recur. Seizures refractory to diazepam and pyridoxine: Induce thiopental coma.	(1–2 g/kg); oral activated charcoal for asymptomatic patients.	
Local anesthetic Bupivacaine • CV: Reductions in cardiac output while blood pressure is maintained; bradycardia, atrio- and intraventricular blocks, ventricular dysrhythmias; CV collapse often refractory to treatment.	Clinical bupivacaine toxicity: • Current ACLS guidelines. AND • IV lipid emulsion (e.g., Intralipid®, Liposyn III® 20%) 1 mL/kg over 1 min; repeat twice more at 3–5-min intervals; then (or sooner if stability is restored) convert to an		Laboratory data and accumulating clinical experience with lipid emulsion therapy in bupivacaine, levobupivacaine, mepivacaine, prilocaine, and ropivacaine toxicity suggest early lipid therapy to attenuate progression of local anesthetic toxic syndrome.

	infusion at a rate of 0.25 mL/kg/min until hemodynamic recovery (>8 mL/kg is unlikely to be useful). OR • IV lipid emulsion (e.g., Intralipid® 20%) 100 mL followed by an infusion 0.5 mL/kg/min. Refractory cardiac arrest: Cardiopulmonary bypass.	Bupivacaine: More cardiotoxic than most other local anesthetics (e.g., lidocaine, ropivacaine, levobupivacaine); earliest signs of cardiac toxicity are prolonged QRS/QTc.
Lidocaine • Neurologic: Numbness of the tongue, light headedness, visual/auditory disturbances, muscular twitching, unconsciousness, seizures, coma, respiratory depression/apnea. • CV: Hypertension and tachycardia (mild intoxication) progressing to bradycardia, hypotension, sinus arrest, heart blocks, intraventricular conduction defects (e.g., prolonged QRS), ventricular dysrhythmias (e.g., ventricular fibrillation), circulatory collapse, asystole.	Clinical local anesthetic toxicity: Current ACLS guidelines and consider IV lipid emulsion therapy (See Bupivacaine) and cardiopulmonary bypass for refractory cardiac arrest.	Lidocaine toxicity: Dose related; neurotoxic manifestations before potentially cardiotoxic levels are reached. Amide local anesthetics may act as oxidizing agents and lead to methemoglobinemia in toxic doses.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Metals Arsenic (As) • Respiratory: Pulmonary edema. • CV: Prolonged QTc and polymorphic ventricular tachycardias (e.g., torsades de pointes). • GI: Abdominal pain, profuse watery stools, hemorrhagic gastroenteritis (hypovolemia shock). • Neurologic: Confusion, delirium, convulsions, encephalopathy, and coma; polyneuropathy (e.g., severe painful burning sensation in soles of feet, ascending weakness and paralysis with neuromuscular respiratory failure). • Hematologic: Reversible bone marrow depression with pancytopenia (particularly	Dysrhythmias: Current ACLS guidelines and avoid class IA/IC antidysrhythmics; limited success with lidocaine, magnesium, and isoproterenol in management of arsenic-induced torsades de pointes; transvenous pacemaker for overdrive pacing. Suspected acute symptomatic As poisoning: IM BAL 3–5 mg/kg every 4 h, gradually tapering to every 12 h over several days; switched to DMSA 10 mg/kg every 8 h for 5 d, reduced to every 12 h for another 2 wk; additional course of treatment may be considered based on posttreatment results: 24-h urinary. As excretion is followed before, during, and after chelation with continued chelation therapy until the urinary As excretion <25 μg/24 h or	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. GI decontamination consideration (after patient stabilized, assessing GI tract integrity and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients; activated charcoal 1–2 g/kg; WBI (See Box 96-2) when evidence of heavy metal burden on abdominal imaging (absence of radiopacities on imaging study is nondiagnostic), monitor effectiveness by serial abdominal imaging studies.	BAL is most effective within hours of ingestion. Monitor respiratory function carefully in patients with progressive sensorimotor dysfunction (e.g., ascending weakness) for impending neuromuscular respiratory failure. Arsenic trioxide: Induction therapy in APL patients receiving daily median arsenic trioxide 0.15 mg/kg (range, 0.06–0.2 mg/kg) infusions over 1–2 h until bone marrow remission or, for a maximum of 60 d, has been associated with QTc prolongation, torsades de pointes, and sudden death. Laboratory diagnosis: Quantitative 24-h urine collection most reliable (spot-urine sample in an emergency); normal *total*

leukopenia), nadir at 1–2 wk with recovery 2–3 wk after the nadir.	during the recovery period when urinary inorganic As concentration <100 μg/24 h or total blood As <200 μg/L.		urinary As values <50 μg/L or <25 μg/24 h; first 2–3 d following acute symptomatic intoxications total 24-h urinary As excretion in excess of several thousand micrograms (spot-urine concentration >1,000 μg/L); recent seafood ingestion may markedly elevate urinary As values for 48 h.
Arsine gas • Latent-onset toxicity (2–24 h). • General: Dizziness, malaise, weakness; dyspnea; vomiting, diarrhea; headache; abdominal pain. • Hematologic: Coombs' negative hemolytic anemia. • GU: Dark-red urine; hemoglobinuria and/or hematuria; renal failure. • Dermatologic: Reddish staining of the conjunctiva; duskily bronzed skin.	Acute and severe arsine poisoning: Exchange transfusion; exchange transfusion *and* hemodialysis in patients with renal insufficiency/failure.	Maximize GFR: See Arsenic.	BAL treatment has been disappointing, does not appear to afford protection against arsine-induced hemolysis.
Iron (Fe) • Stage 1 (GI toxicity): Abdominal pain, vomiting, diarrhea,	Symptomatic patient (e.g., recurrent vomiting or diarrhea, acidosis, shock, and decreased level of	Maximize GFR with IV NS, and target urine output 2–4 mL/kg/h.	An orderly progression through all stages may not occur; fatalities possible without significant

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
hematemesis, and hematochezia; variable severity; latent toxicity with enteric-coated tablets. • Stage 2 (relative stability): Apparent improvement in clinical status, but not completely asymptomatic; careful assessment and repeated monitoring will document some degree of hypovolemia, circulatory shock, and acidosis. • Stage 3 (circulatory shock): Hypovolemic, distributive, or cardiogenic; metabolic acidosis usually precedes circulatory shock. • Stage 4 (hepatotoxicity): Liver failure. • Stage 5 (GI scarring): Most common area is gastric outlet; obstruction.	consciousness or coma) regardless of serum Fe concentration or asymptomatic patient with serum Fe concentration ≥500 µg/dL (90 µmol/L): IV deferoxamine initiated slowly and gradually increased to 15 mg/kg/h over 20–30 min and continued for 24 h; continuous IV deferoxamine therapy >24 h (rarely needed) is interrupted for 12 of every 24 h; end points in treatment include resolution of systemic signs/symptoms, correction of acidosis, and return of urine color to normal (if patient developed vin rosé–colored urine during therapy).	GI decontamination consideration ((after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): • Gastric lavage (See Box 96-1) in acutely sick patients; WBI (See Box 96-2) when evidence of a heavy metal burden on abdominal imaging (absence of radiopacities on imaging study is nondiagnostic) or history of elemental iron ingestion >1.5 g (Peds: >60 mg/kg), monitor effectiveness by serial abdominal imaging studies. • Bezoar/concretion: Procedural removal if WBI ineffective.	GI involvement; hepatotoxicity may be absent in otherwise severe poisoning; presenting signs and symptoms depend on the time since ingestion. Serum Fe concentration: • Validates the ingestion, guides management, and provides prognostic information. • Blood sampling to determine peak serum concentration should be 4–6 h after an overdose of conventional tablets and several hours later for modified release formulations; serial serum Fe concentration determinations every 2 h until a definite downward trend is established. • Peak <500 µg/dL (90 mmol/L) usually associated with negligible-to-mild systemic

toxicity; there may be significant GI symptoms.
- Peak 500–1,000 µg/dL (90–180 µmol/L) associated with moderate systemic toxicity.
- Peak >1,000 mg/dL (180 mmol/L) associated with severe toxicity (e.g., profound acidosis, shock, hepatotoxicity, and coma); mortality rate approaches 100% when >10,000 µg/dL (1,800 µmol/L).

Acidosis is the first objective indicator of systemic toxicity, pH <7.30 indicative of significant toxicity. The total iron-binding capacity (TIBC) is falsely elevated in the presence of high serum Fe concentrations and is unreliable during hyperferremic states; a serum Fe concentration <TIBC does *not* rule out acute iron poisoning.

Pregnant patients: Consequences of Fe toxicity

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
Iron (Fe) (*continued*)			same as in other patients; fetus is relatively protected, and its health depends on maternal health; treatment same as that given a nonpregnant patient. Adverse drug events from deferoxamine therapy: Tachycardia, hypotension, shock, and a generalized beet red flushing of the skin, blotchy erythema, and urticaria; acute renal failure when deferoxamine is administered to hypovolemic patients; pulmonary toxicity (e.g., ARDS) associated with IV therapy over several days; patients receiving deferoxamine at risk for *Yersinia* infections.
Lead (Pb) • Constitutional symptoms: Fatigue, arthralgias, decreased libido, irritability,	Seizures: IV BZD or phenobarbital. Symptomatic Pb encephalopathy: IM BAL is 75 mg/m^2 (3–5 mg/kg)	GI decontamination consideration (after patient stabilized precautionary measures to minimize	CT head scan in patients with encephalopathy to rule out cerebral edema.

impotence, depression, anorexia, malaise, myalgias, weight loss, and insomnia.
- GI: Constipation or diarrhea; intestinal spasm with severe, excruciating, paroxysmal, abdominal pain (i.e., "lead colic").
- Neurologic: Impaired concentration, visual-motor coordination, headache; encephalopathy characterized by vomiting, tremors, hyperirritability, ataxia, confusion, delirium, lethargy, obtundation, seizures, coma; children may exhibit SIADH; peripheral motor neuropathy predominantly affecting upper extremities (e.g., "wrist drop").
- Hematologic: Normochromic or microcytic anemia, may be accompanied by basophilic stippling of erythrocytes.

every 4 h. After 4 h have elapsed since the priming dose of BAL, start IV CaEDTA 1,500 mg/m^2/d (30 mg/kg/d). In cases of cerebral edema and/or increased intracranial pressure associated with encephalopathy, administer CaEDTA (same dosage) by deep IM injection (extremely painful) along with procaine 0.5% in 2–3 divided doses every 8–12 h. Continue BAL and CaEDTA 5 d. Cessation of chelation is often followed by a rebound in blood Pb concentration; a second chelation course may be considered based on whole-blood Pb concentration after 2 days' interruption of BAL and CaEDTA treatment, and the persistence or recurrence of symptoms. A third course may be required if the whole-blood concentration rebounds ≥50 mg/dL within 48 h after second chelation treatment. If chelation is required for the third time, it should begin a week after the last dose of BAL and CaEDTA.

aspiration): See Arsenic; omit activated charcoal.

Surgically remove Pb-containing foreign body in or adjacent to synovial space, if possible.

Child with encephalopathy: Establishing adequate urine output by IV infusion 10–20 mL/kg of 10% dextrose in water over 1–2 h. If this fails to produce a urine output, infusion 1–2 g/kg of a 20% mannitol solution 1 mL/min. Once urine output has been established, IV fluids should be restricted to the calculated basal water and electrolyte requirements plus a careful assessment of continuing losses; indwelling Foley catheter to monitor rate of urine formation; titrate IV fluids hourly to maintain urine flow within basal metabolic limits (i.e., 0.35–0.50 mL of urine secreted per calorie metabolized per 24 h or 350–500 mL/m^2/24 h).

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Lead (Pb) (*continued*)	Symptomatic patients who are not overtly encephalopathic: IM BAL 50 mg/m² (2–3 mg/kg) every 4 h. After 4 h have elapsed since the priming dose of BAL, start IV CaEDTA 1,000 mg/m²/d (20–30 mg/kg/d) or in 2–3 divided doses every 8–12 h. BAL and CaEDTA should be continued for 5 d with daily monitoring of whole-blood Pb concentrations. BAL may be discontinued any time during these 5 d if the whole-blood Pb level <50 μg/dL, but CaEDTA treatment should continue for 5 d. Cessation of chelation often followed by rebound in blood Pb concentration. A second or third course of chelation may be considered based on the same guidelines as in the previous paragraph. Asymptomatic patients with whole-blood Pb levels		

	≥70 μg/dL: BAL and CaEDTA in the same doses and with the same guidelines as for treatment of symptomatic Pb poisoning without encephalopathy. A second course of CaEDTA chelation alone may be necessary if whole-blood Pb concentration rebounds ≥50 μg/dL within 5–7 d after chelation has ceased. Alternative: Oral DMSA 10 mg/kg (350 mg/m²) every 8 h for 5 d and then every 12 h for 2 wk. Additional course of treatment may be considered based on posttreatment whole-blood Pb concentrations and the persistence or recurrence of symptoms. An interval ≥2 wk may be indicated to assess the extent of posttreatment rebound in whole-blood Pb concentration. Cerebral edema: Current guidelines.		
Lithium (Li) Acute effects • Mild intoxication: Lethargy, fatigue, memory impairment, fine tremor.	Asymptomatic or mild/moderate toxicity: Maximize GFR with IV NS and target urine output 2–4 mL/kg/h if renal Li clearance (urine Li [mmol/L]/serum Li [mmol/L] ×	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick	Acute overdose: Minor neurologic manifestations despite high serum Li concentration (e.g., 9.0 mmol/L) during initial 12 or more hours; toxicity

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• Moderate intoxication: Confusion, agitation, delirium, coarse tremor, hyperreflexia, hypertension, tachycardia, dysarthria, nystagmus, ataxia, muscle fasciculations, extrapyramidal syndromes, choreoathetoid movements. • Severe toxicity: Bradycardia, coma, seizures, hyperthermia, hypotension. Permanent sequelae include choreoathetosis, nystagmus, ataxia. • CV: Bradycardia; sinoatrial block; intraventricular conduction defects (e.g., prolonged QRS/QTc in severe toxicity); ECG changes similar to hypokalemia. • Metabolic: Hypercalcemia; hypermagnesemia; nonketotic hyperglycemia; transient DKA; goiter; hypothyroidism rare.	urine flow rate [mL/min]) <15–30 mL/min; furosemide and forced diuresis are of unproven efficacy.	patients; WBI (See Box 96-2) for large ingestion of modified release formulation; procedural removal of bezoar/concretion. Hemodialysis consideration: • Severe clinical toxicity (e.g., neurologic dysfunction). • Renal dysfunction. • Patient becomes clinically unstable or not improving. • Satisfactory Li clearance (≥15–30 mL/min) cannot be achieved. • Patient unlikely to tolerate a target urine output 2–4 mL/kg/h (e.g., marginal cardiopulmonary reserve). • Probability patient will become toxic or develop permanent neurologic deficits (e.g., progressive/worsening peripheral neurologic dysfunction such as tremors, fasciculations, and clonus).	may develop over subsequent 24–48 h even as serum concentration falls; serum Li concentration cannot predict toxicity or guide therapy; no clinical variable accurately predicts which patients will deteriorate; a reduced or absent anion gap may occur with severe Li carbonate toxicity. Chronic toxicity • CNS: Mild effects associated with serum Li concentrations <1.5 mmol/L, mild/moderate effects 1.5–3.0 mmol/L, severe/death >3–4 mmol/L. NDI does not respond to vasopressin, but may improve with amiloride, hydrochlorothiazide, carbamazepine, or indomethacin; indomethacin may be more effective in the acute setting.

• GU: Nephrogenic diabetes insipidus (NDI); sodium-losing nephritis.		• Acute asymptomatic poisoning and serum Li >9 mmol/L). • Symptomatic patients with chronic serum Li >2.5 mmol/L. Hemodialysis should be repeated until serum Li concentration drawn 6–8 h after last dialysis is ≤1 mmol/L; CAVH/CVVH may be useful in attenuating rebound effect after hemodialysis or in asymptomatic patients with high/raising serum Li levels.	Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVH may be the only option in hypotensive patients until hemodialysis can be tolerated.
Mercury (Hg) Elemental Hg vapor • Systemic effects: Fever, chills, headache, dyspnea, gingivostomatitis, vomiting, paroxysmal cough, tachypnea, chest tightness, diarrhea, abdominal cramps. • Respiratory: Interstitial pneumonitis, pulmonary infiltrates, noncardiogenic pulmonary edema, interstitial pulmonary fibrosis; complications include SC emphysema, pneumomediastinum, and pneumothorax.	Supportive care. Chelation: • No proven effect on improving clinical outcome. • Oral DMSA (10 mg/kg every 8 h, tapering to every 12 h over the next several days, and continued until urinary Hg concentration approaches background) may enhance urinary Hg excretion and reduce nephrotoxicity after GI absorption of elemental Hg. • BAL may redistribute Hg to the brain.		Neurologic: Toxicity typically a result of *chronic* exposure. Confirming elemental Hg exposure: 24-h urinary Hg excretion (reference: <15 µg/24 h) most useful tool in diagnosing acute exposure; reference whole-blood Hg concentration <2 µg/dL and "spot" urine Hg concentration <10 µg/L.

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
Inorganic Hg (e.g., mercuric chloride) • GI: Corrosive stomatitis, abdominal pain, hemorrhagic gastroenteritis, necrotizing esophagitis, gastritis, and ulcerative colitis. • GU: Acute renal failure.	Suspected acute inorganic Hg poisoning: BAL and DMSA; See Arsenic.	Maximize GFR: See Arsenic. GI decontamination (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): See Arsenic. Endoscopy if corrosive injury (e.g., stridor, drooling, dysphagia, abdominal pain) is suspected.	BAL is most effective within 4 h of ingestion. Confirming inorganic Hg exposure: See Elemental Hg; whole-blood Hg concentrations >50 μg/dL in acute poisoning associated with gastroenteritis and acute renal tubular necrosis.
Organic Hg (e.g., methylmercury) • Latent onset (weeks to months); paresthesias, hearing impairment, progressive incoordination, loss of voluntary movement, mental retardation. • Classic triad of methylmercury poisoning: Dysarthria, ataxia, and constricted visual fields.	Supportive care. Chelation: • No proven effect on improving clinical outcome. • DMSA appears promising in animal studies; See Elemental Hg.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1); oral (repeated doses) polythiol resin.	Confirmatory organic Hg exposure: Whole-blood Hg concentrations >20 μg/dL associated with symptoms; urinary Hg concentration not useful.

Methylxanthine Caffeine • GI: Nausea, vomiting; hematemesis. • Neurologic: Anxiety, agitation; seizures. • Metabolic: Hypokalemia, hyperglycemia; metabolic acidosis. • CV: Dysrhythmias; myocardial infarction. • Musculoskeletal: Rhabdomyolysis.	Management of caffeine toxicity similar to theophylline toxicity.	GI decontamination consideration: See Theophylline. Hemodialysis consideration: Seizures, cardiac dysrhythmias, or serum caffeine concentrations >100 μg/mL.	Life-threatening events associated with serum concentrations >100 μg/mL; seizures have occurred at 50 μg/mL; death has been reported at 80 μg/mL; 385 μg/mL has been associated with survival.
Theophylline • CV: Sinus tachycardia, ventricular irritability/dysrhythmias; hypotension with widened pulse pressure and increased cardiac index (i.e., marked fall in SVR). • Neurologic: Hyperventilation; agitation and anxiety; vomiting; seizures. • GI: Vomiting, diarrhea; hematemesis. • Musculoskeletal: Tremors, myoclonic jerks.	Vomiting: IV ondansetron 8 mg (Peds: 0.2 mg/kg, max 8 mg) or IV metoclopramide 1 mg/kg (Peds: 0.1 mg/kg, max 1 mg/kg). Sinus tachycardia, supraventricular tachyarrhythmias, ventricular irritability: IV propranolol 1–3 mg and then 1 mg every 5–10 min (Peds: 0.02 mg/kg, not to exceed adult dose) until dysrhythmias corrected; potential hazard is bronchospasm; IV esmolol 500 μg/kg over 1 min followed by 25–200 μg/kg/min infusion; consider IV adenosine 6 mg, escalate	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): • WBI (See Box 96-2) for large ingestion of modified release formulation. • Procedural removal of bezoar/concretion. • Activated charcoal 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) until serum theophylline <15 μg/mL; alternatively,	Alteration in theophylline clearance: CYP1A2 and CYP 3A4 inhibitors (e.g., erythromycin, clarithromycin, ciprofloxacin, cimetidine), heart failure, liver disease decrease clearance; barbiturates, carbamazepine and polyaromatic hydrocarbons of cigarette smoke, hyperthyroidism, cystic fibrosis increase clearance. Risk stratification • Acute toxicity: Serum theophylline 20–40 μg/mL:

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• Metabolic: metabolic acidosis; hypokalemia, hyperglycemia, hypophosphatemia, hypomagnesemia, hypercalcemia.	to 12 mg (Peds: 50-100 mg/kg and increase by 40 mg/kg increments, not to exceed adult dose) if needed. Ventricular irritability with hemodynamic compromise: IV lidocaine 1.5 mg/kg at 50 mg/min followed by infusion 2–4 mg/min (Peds: 1 mg/kg over 2 min followed by infusion 15–50 μg/kg/min); pulseless ventricular tachycardia or fibrillation: IV amiodarone 5 mg/kg over 5 min. Hypotension with a wide pulse pressure: IV crystalloid bolus, propranolol, vasopressor (e.g., phenylephrine, norepinephrine). Seizures: IV BZD, progress to thiopental or pentobarbital, and neuromuscular blockade and general anesthesia.	0.25–0.5 g/kg/h via continuous nasogastric infusion; not in patients with decreased bowel sounds/ileus. Hemodialysis consideration: • Before the onset of life-threatening events, hemodynamic instability or repeated seizures. • Acute intoxication and serum theophylline >80 μg/mL. • Patients <6 mo or >60 y with chronic overmedication and serum theophylline >30 μg/mL. • Patient with moderate toxicity and unable to tolerate activated charcoal therapy. Exchange transfusion used successfully in neonates with severe toxicity.	nausea, vomiting, tachycardia; 40–70 μg/mL: premature ventricular contractions, agitation, tremors; >80 μg/mL: cardiac dysrhythmias, intractable seizures. • Chronic overmedication: Neonates or elderly patients (e.g., >75 y) with underlying cardiac disease and/or take medications that inhibit theophylline metabolism; no correlation between serum theophylline concentration and appearance of life-threatening events (e.g., severe intoxication at steady-state serum theophylline concentrations as low as 20–30 μg/mL and seizures as low as 17 μg/mL). • Acute-on-therapeutic theophylline toxicity: Serum

				theophylline concentrations >60 μg/mL: life-threatening events. Hypokalemia predominantly results as intracellular potassium shift with minimal total body potassium loss. Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVT may be the only option in hypotensive patients until hemodialysis can be tolerated.
NSAID Aspirin (acetylsalicylic acid, ASA) • Metabolic: Respiratory alkalosis (hyperpnea/tachypnea), respiratory alkalosis/metabolic acidosis/aciduria, metabolic acidosis/respiratory acidosis/aciduria; anion gap metabolic acidosis; hypokalemia; hyperthermia. • Respiratory: Respiratory insufficiency/failure; acute lung injury/noncardiogenic pulmonary edema.	Signs and symptoms consistent with salicylate toxicity, serum ASA >30 mg/dL (2.17 mmol/L) after acute overdose: • Fluid resuscitation. AND • Urine alkalinization: IV sodium bicarbonate 2 mmol/kg bolus followed by continuous infusion of sodium bicarbonate 150 mmol mixed in 1,000 mL D5W starting at 1.5–2.0 times the maintenance rate, titrate to	Maximize GFR: IV NS target urine output 2–4 mL/kg/h; IV fluids should contain at least 50 g/L (5%) glucose, minimum 100 g/L (10%) glucose when hypoglycemia/CNS symptoms are evident. GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) followed by oral activated charcoal (1–2 g/kg) following	Done nomogram not useful; carbonic anhydrase inhibitors (e.g., acetazolamide) contraindicated; delayed onset and progression of toxicity with enteric-coated/sustained-release tablets; nonacute/chronic intoxication masquerade as SIRS, acute abdomen, ACS/AMI, encephalopathy/encephalitis, alcohol intoxication/withdrawal, organic psychosis, sepsis, dementia or delirium, DKA.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
• Neurologic: Agitation; slurred speech; altered mental status; hallucinations; encephalopathy; seizures; coma.	maintain urinary pH 8.0 and arterial pH <7.55; assess clinical status/laboratory parameters (e.g., electrolytes, acid–base, urine pH) hourly; terminate when clear clinical–biochemical recovery and serial decline in serum ASA concentration toward therapeutic range. AND • Potassium replacement/supplement. Respiratory insufficiency/failure: Adjust ventilator minute volume to maintain PCO_2 to at least patient's preintubation PCO_2 and arrange for urgent hemodialysis. Pulmonary edema: Management same as acute lung injury/ARDS, and arrange for urgent hemodialysis. Hyperthermia: External cooling.	serious overdose; otherwise, oral activated charcoal; WBI (See Box 96-2) for large ingestion of modified release formulation; endoscopic removal of bezoar/concretion. Consider hemodialysis when serum salicylate >90 mg/dL (6.52 mmol/L), need for endotracheal intubation, chronic salicylism, persistent aciduria, clinical deterioration, altered mental status, patients with comorbidities (e.g., heart failure, chronic obstruction pulmonary disease), pulmonary edema, persistent acidemia, persistent hypotension, coagulopathy, renal/hepatic dysfunction, extremes of age, seizures; *urgent hemodialysis* in patients needing endotracheal intubation, with chronic salicylate toxicity, altered mental status, persistent acidemia, comorbidities, elderly patients.	Urine alkalinization: Not a substitute for hemodialysis; success in patients treated early in the course of poisoning and not severely toxic/acidotic; contraindication: severe ASA toxicity, renal/heart failure, cerebral/pulmonary edema, arterial pH >7.55; complication: hypokalemia, hypocalcemia, fluid/sodium overload, pulmonary edema, tetany. Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVH may be the only option in hypotensive patients until hemodialysis can be tolerated.

Other NSAID Ibuprofen • Metabolic acidosis, ARDS, renal failure, coma, seizures, GI bleeding, cholestasis, hepatotoxicity, thrombocytopenia, hypothermia, shock; meningoencephalitis (aseptic meningitis) with therapeutic dosing.	Supportive care.		
Mefenamic acid • Muscle twitching, tonic–clonic seizures, apnea, coma, cardiac arrest.	Supportive care.		
Phenylbutazone • GI: *Predominately* latent hepatotoxicity (12–24 h), and may be only manifestation of severe toxicity. • GU: Red urine (pyrazolone metabolite: rubazonic acid) may be observed. • CNS: Progressive impairment of consciousness with coma and seizures. • Sudden respiratory arrest followed by cardiac arrest.	Supportive care.	Adjunct hemoperfusion with uncoated amberlite XAD-4 resin in cases with a poor prognosis.	Phenylbutazone was withdrawn from the U. S. market 1970s, still available from veterinary sources and other countries.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Opioid			
General: Coma, miosis, respiratory depression, decreased GI motility. • Dextromethorphan: Serotonin syndrome from MAOI interaction; long-term use may result in bromide toxicity. • Diphenoxylate: Recurrent respiratory/CNS depression. • Fentanyl: Rapid IV administration may result in acute myoclonic truncal/chest wall rigidity impairing respiration. • Heroin: Noncardiogenic pulmonary edema, cardiac conduction abnormalities/dysrhythmias; inhalation of heated heroin vapors (i.e., "chasing the dragon") associated with progressive spongiform leukoencephalopathy.	Respiratory depression/failure: IV naloxone 0.04–0.1 mg if opioid dependent, otherwise 2 mg; 10–20 mg may be required for high-potency opioids (e.g., methadone, pentazocine, propoxyphene, diphenoxylate); repeat IV naloxone boluses may be required every 20–60 min. Therapeutic IV naloxone infusion: Multiply the effective naloxone bolus dose by 6.6, adding that quantity to 1,000 mL NS, infuse solution at 100 mL/h, titrated to maintain adequate spontaneous ventilation without precipitating opioid withdrawal; empirically continued for 12–24 h and carefully observed for 2–4 h for recurrent respiratory depression after discontinuing naloxone		Naloxone: Goal is to reestablish adequate spontaneous ventilation; intralingual/endotracheal/intraosseous administration acceptable if no immediate IV access; IM/SC less desirable in urgent situation. Diphenoxylate: Formulated with atropine (Lomotil®); decreased GI motility and difenoxin (metabolite) accumulation, a potent opioid with a long half-life. Heroin may be "cut" with amphetamine, cocaine ("speed ball"), scopolamine, and naloxone therapy may "unmask" sympathomimetic or anticholinergic toxicity. Propoxyphene: Available alone or in combination with

- Meperidine: Seizures from normeperidine (metabolite) accumulation (e.g., renal impairment); acute parkinsonism following contaminated analog MPPP use; fatal interaction with MAOI (serotonin syndrome).
- Methadone: Exceptionally prolonged duration of action (average half-life 25 h, may be 52 h during long-term therapy); aassociation between high daily methadone dose (mean 397 ± 283 mg) and torsades de pointes (mean QTc 615 ± 77 ms).
- Propoxyphene: Rapidly progressive cardiac dysrhythmias, circulatory collapse, seizures, respiratory arrest.
- Tramadol: Seizures; serotonin syndrome.

infusion; allow naloxone to abate in acute iatrogenic opioid withdrawal.

Spongiform leukoencephalopathy: Supportive; coenzyme Q 30 mg qid, vitamin E 2,000 mg every d, and vitamin C 2,000 mg every d have been advocated.

Seizures: Current guidelines; adjunct naloxone therapy may be effective in propoxyphene, but not meperidine or tramadol seizures; reported immediately following naloxone administration for tramadol overdose.

Serotonin syndrome: See Antidepressants.

acetaminophen or ASA; withdrawn from the US market at the request of the US Food and Drug Administration (19 November 2010).

Complications include rhabdomyolysis, hyperkalemia, myoglobinuria, renal failure.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Pesticides Aluminum phosphide Ingestion • GI: Retrosternal burning, epigastric discomfort; recurrent profuse vomiting; watery diarrhea; GI bleed; jaundice with abnormal liver function tests. • CV: Hypotension with clear mental status; shock (heart rate inappropriately slow for degree shock); myocardial injury; dysrhythmias, intraventricular conduction disturbances; global left ventricular and interventricular septum hypokinesia with decreased ejection fraction; pericarditis (rare). • Respiratory: Tachypnea; ARDS. • Metabolic: Metabolic acidosis; hypomagnesemia; hyperkalemia.	Supportive care. IV hydrocortisone 400 mg every 4–6 h or IV dexamethasone 4 mg every 4 h, IV H_2 receptor antagonist (e.g., ranitidine), IV proton pump inhibitor (e.g., omeprazole) have been advocated. Cardiac dysrhythmias or hypomagnesemia: IV magnesium 1–6 g over 30 min followed by infusion 0.5–2 g/h has been advocated.	Prevent secondary contamination and poisoning with appropriate precautionary measures. GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) with a solution of 1:5,000 potassium permanganate (remove and oxidize unabsorbed aluminum phosphide); nasal gastric 2% bicarbonate solution (minimize phosphine release).	A strong suspicion of aluminum phosphide poisoning when vomitus has typical rotten fish odor. Silver nitrate test on stomach contents (5 mL) mixed with 15 mL water placed in a flask, round strip of filter paper impregnated with silver nitrate (0.1 N) is placed on the mouth of flask and is heated to 50°C for 15–20 min, filter paper strip is then dried; phosphine's presence blackens silver nitrate paper. Insufficient clinical evidence to mandate steroid and magnesium therapy. Toxicity can occur as a result of inhalation of phosphine gas released when phosphide contacts water.

Anticoagulant (e.g., warfarin, superwarfarin) • Cutaneous bleeding, soft tissue ecchymosis; gingival bleeding; epistaxis; hematuria; menorrhagia; hemoptysis; GI, peritoneal, diffuse alveolar, ICH.	Patients with or suspected major anticoagulant-related hemorrhage or INR >20 • IV prothrombin complex concentrate (PCC) 50 U/kg *or* IV fresh frozen plasma (FFP) 10–20 mL/kg *or* IV recombinant activated factor VII (rFVIIa) 15–90 μg/kg. AND • IV vitamin K_1 10 mg (diluted with 5% dextrose, 0.9% sodium chloride, or 5% dextrose in 0.9% sodium chloride; administered at ≤1 mg/min; be prepare to treat anaphylaxis) *or* oral/nasogastric vitamin K_1 7 mg/kg/d divided every 6 h. Discontinue Vitamin K_1 therapy at an arbitrary time, obtain serial INR/PT and restart vitamin K_1 when INR/PT is elevated or monitor serum factor VII concentration and restart vitamin K_1 when a progressive decrease in factor VII levels to 30% of normal *or* serum brodifacoum concentration <10 ng/mL *or* when serum vitamin K	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg.	PCC: Contraindicated in disseminated intravascular coagulation and uncompensated liver disease; adverse drug events include thrombosis, disseminated intravascular coagulation, blood-borne pathogens transmission, allergic reactions. rFVIIa: Unlikelihood of blood-borne pathogen transmission, obviates volume constraints of FFP administration, reduces time for administration and achieving adequate hemostasis.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Anticoagulant (e.g., warfarin, superwarfarin) (*continued*)	2,3-epoxide concentration begins to fall. Patient on warfarin with excessive INR and without bleeding • INR <5.0: Lower dose *or* omit next warfarin dose. • INR 5.0–9.0: Discontinue warfarin for several doses; high risk (e.g., age, recent hemorrhage, alcoholism, hepatic or renal impairment, and NSAID use) omit next warfarin dose *and* administer oral vitamin K_1 1.0–2.5 mg *or* IV vitamin K_1 0.5–1.0 mg. • INR 9.0–20.0: Oral vitamin K_1 3.0–5.0 mg. • INR >20.0: IV vitamin K_1 10 mg and PCC *or* FFP *or* rFVIIa *and* repeat vitamin K_1 doses every 12 h as needed.		

Methyl bromide • Neurologic: Vomiting; headache, gait disturbance, vertigo, visual disturbance (premonitory stage); "Jerkiness," intentional tremors, action myoclonus, seizures, delirium, acute mania (cerebral irritation stage); hallucinations, apathy, amnesia, aphasia, incoordination (recovery stage, may last years). • Respiratory: Dyspnea; bronchitis; pulmonary edema; pneumonitis; respiratory failure. • GU: Proteinuria; hematuria; renal failure. • Liver: Jaundice; liver function test abnormalities. • Skin: Burns (underlie clothes and gloves where methyl bromide gas is trapped).	Supportive care.	Remove all clothing, wash skin with soap and water to eliminate potential methyl bromide residues. Early hemodialysis associated with improving mortality.	Serum bromide concentration: • Poor surrogate for methyl bromide. • May confirm, but does not correlate with severity of exposure. • Significantly elevated concentrations may be seen as an elevated chloride level. Spectrophotometric method may be more useful in detecting methyl bromide in biologic fluid matrix.
N-3-Pyridylmethyl-*N'*-p-nitrophenylurea (PNU; Vacor Rat-Killer) • Nausea, vomiting, abdominal pain, perforation (corrosive	Known or suspected PNU exposure: IV or IM niacinamide (nicotinamide) 500 mg followed by 100–200 mg every 4 h for up to 48 h, increased to every	GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): Gastric lavage (See	Administer niacin as a substitute when niacinamide (nicotinamide) is unavailable; vasodilatory effects may exacerbate hypotensive effects

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
effects); hypoglycemia followed by hyperglycemia and ketoacidosis accompanied by severe postural hypotension and sensorimotor peripheral and autonomic neuropathies.	2 h if signs of toxicity develop, maximum total dose 3 g/d for adult (Peds: one-half of adult dose); when patient able to take oral medications 100 mg three to five times daily for 2 wk. Postural hypotension: Limited response to oral fludrocortisone 0.3 mg/d and elastic stockings.	Box 96-1) in patients presenting soon after a serious ingestion followed by oral/nasogastric activated charcoal 1–2 g/kg *provided no clinical evidence of serious caustic effect on the GI tract.*	of PNU, causes and exacerbates glucose intolerance, less effective than niacinamide; niacinamide in capsule form may be found at nutritional supplement outlets. Monitor serum glucose closely and treat hypoglycemia with glucose supplementation; management of subsequent hyperglycemia and ketoacidosis same as diabetes mellitus and DKA.
N,N-Diethyl-m-toluamide (diethyltoluamide or DEET) • Neurologic: Anxiety; behavioral changes; tremors; lethargy; ataxia; confusion; seizures; coma. • Skin: Irritation, contact dermatitis, urticaria; skin necrosis. • Immunologic: Anaphylactic reactions with cutaneous application.	Supportive care. Seizures: IV BZD, progress to barbiturate.	Decontamination consideration: Remove all clothing, and meticulously wash skin with soap and water.	

Organochlorine [e.g., dichlorodiphenyl trichloroethane (DDT) and related agents, hexachlorocyclohexanes, the cyclodienes (e.g., chlordane, heptachlor, endrin, aldrin, and dieldrin), and toxaphenes] • GI: Nausea, vomiting, and diarrhea, especially if petroleum distillate additives/vehicles. • Respiratory: Aspiration resulting in tachypnea, respiratory distress, pulmonary edema; hypersensitivity pneumonitis following inhalation of organochlorine mixed with pyrethrins. • Neurologic: Psychomotor agitation, CNS depression, opisthotonos, slurred speech, muscle tremors, weakness; seizures with or without a prodrome and may be delayed following ingestion or dermal absorption. • CV: Cardiac dysrhythmias.	Seizures: IV BZD, progress to barbiturate, neuromuscular paralysis, and general anesthesia; phenytoin not effective and may exacerbate seizures. Bronchospasm: Humidified oxygen and nebulized bronchodilators; parenteral adrenergic amines may potentiate myocardial irritability.	Decontamination consideration: • Precautionary measures to prevent secondary contamination; completely disrobe, remove all jewelry/accessories, meticulously wash entire body with soap and water including hair and fingernails; discard all wash water in a secure fashion; place clothing and leather goods in a plastic bag labeled "biohazard" for disposal. • Chlordecone: Oral/nasgastric cholestyramine 4 g every 6 h.	Systemic toxicity by ingestion, dermal absorption, or inhalation. Chlorinated hydrocarbons are radiopaque, and directly related to the number of chlorine atoms per molecule.

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
• Acute DDT exposures presents with tremors, nausea, vomiting, muscle weakness, and confusion, progressing to seizures.			
Organophosphate (cholinergic agents) • HEENT: Miosis, lacrimation, rhinorrhea, salivation. • Respiratory: Bronchial muscle spasm, pulmonary edema, respiratory failure. • CV: Hypertension/hypotension; dysrhythmias. • GI: Diarrhea, vomiting; abdominal pain; pancreatitis. • Neurologic: Seizures, coma, delirium, Cheynes-Stokes respiration. • Musculoskeletal: Fasciculations, dystonias, choreoathetoid movements, paralysis. • Skin: Diaphoresis.	Seizures: IV atropine and BZD (e.g., diazepam 0.2–0.4 mg/kg or lorazepam 0.05 mg/kg) *or* phenobarbital 18 mg/kg. Cholinergic crisis: • Respiratory support. AND • IV atropine 1–4 mg (Peds: 0.05 mg/kg), double the dose every 5–10 min as needed until pulmonary secretions are controlled (tachycardia is *not* a contraindication to atropine); once stabilized, start atropine infusion (10%–20% of total dose for stabilization per hour) and then titrated back the infusion; restart atropine at the first signs of cholinergic excess.	Decontamination: Precautionary measures to prevent secondary contamination; completely disrobe; remove all jewelry/accessories; meticulously wash entire body with soap and water, including hair and fingernails; discard all wash water in a secure fashion; place clothing and leather goods in a plastic bag labeled "biohazard" for disposal.	Cholinergic poisoning is a *clinical diagnosis* based on a history of exposure, presence of a cholinergic toxidrome, and clinical improvement after appropriate antidotal therapy; plasma (pseudocholinesterase) and red blood cell cholinesterase activity to confirm clinical diagnosis. Atropine has no effect on muscle weakness or paralysis and will not affect acetylcholinesterase regeneration rate; pralidoxime regenerates acetylcholinesterase and is most effective when initiated early; respiratory muscles are the *last* to recover.

- Metabolic: Hyperglycemia/hypoglycemia.
- Intermediate syndrome: Associated with severe organophosphate toxicity; conscious patient without fasciculation or other cholinergic signs (apparent recovery from acute cholinergic crisis) developing marked weakness of neck flexion and varying degree of motor cranial nerve, proximal limb muscle (e.g., shoulder abduction, hip flexion), and respiratory muscle weakness 24–96 h after poisoning, lasting 5–18 d.

AND

- IV pralidoxime 30 mg/kg over 30 min followed by a continuous infusion 8–10 mg/kg/h with empiric dose adjustment based on clinical response; continue until atropine has not been required for 24–48 h and patient extubated; restart pralidoxime if recurrent signs/symptoms.

Agitation: Review atropine dosing; IV BZD.

Review respiratory function frequently after atropine/pralidoxime/extubation: Intubate/ventilate if tidal volume <5 mL/kg, vital capacity <15 mL/kg, apneic events, or PaO_2 < 60 mm Hg on FIO_2 > 60%.

Intermediate syndrome: Regularly assess flexor neck strength by asking patient to lift their head off the bed and hold it while pressure is applied to their forehead; any weakness suggests at risk

Succinylcholine use may result in prolonged (hours to days) paralysis.

Carbamates and other reversible cholinesterase inhibitors: Signs/symptoms should resolve within 24 h; atropine *and* pralidoxime have been used to treat acutely ill patients with carbamate toxicity unless carbaryl (Sevin) is known to be involved, then just atropine and supportive care.

Latent-onset toxicity following fenthion, parathion, dichlofenthion, leptophos poisoning; recurrence of cholinergic crises (release of fat-soluble organophosphorus from fat stores) days to weeks after ingestion will need retreatment with atropine and pralidoxime.

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
Organophosphate (cholinergic agents) (*continued*)	of developing respiratory failure; assess respiratory function at least every 4 h, and intubate/ventilate if tidal volume <5 mL/kg, vital capacity <15 mL/kg, or PaO_2 <60 mm Hg on FIO_2 >60%.		
Pentachlorophenol • Tachycardia, tachypnea, sweating, altered consciousness, hyperthermia, seizures; pulmonary edema, intravascular hemolysis, pancreatitis, jaundice, acute renal failure.	Supportive care and vigorous management of hyperthermia. Known or symptomatic pentachlorophenol poisoning: Urine alkalinization with IV sodium bicarbonate 2 mmol/kg bolus followed by continuous sodium bicarbonate infusion (150 mmol mixed in 1,000 mL D5W) starting at 1.5 to 2.0 times the maintenance rate, titrate to maintain urinary pH 8.0 and arterial pH < 7.55; reassess clinical status/laboratory parameters (e.g., electrolytes, acid–base, urine pH) hourly; terminate when clear clinical–biochemical recovery.	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. Decontamination consideration: Remove all clothing, wash skin with soap and water; gastric lavage (after patient stabilized and precautionary measures to minimize aspiration) in acutely sick patients (See Box 96-1); oral/nasogastric cholestyramine 4 g every 6 h. Exchange transfusion used successfully in infants with severe toxicity.	There is no antidote for pentachlorophenol poisoning and insufficient clinical evidence to mandate routine urine alkalinization or cholestyramine use.

Pyrethroid • Neurologic: Paresthesias; fasciculations; coma; seizures. • Acute hypersensitivity reactions (e.g., anaphylaxis). • Respiratory: Hypersensitivity pneumonitis following inhalation of organochlorine mixed with pyrethrins.	Seizures: See Organochlorine. Bronchospasm: See Organochlorine.		Systemic toxicity by ingestion, dermal absorption, or inhalation.
Sodium monofluoroacetate (compound 1080) and sodium fluoroacetamide (compound 1081) • GI: Nausea, vomiting, and abdominal pain. • Neurologic: Anxiety, verbosity, irritability, agitation, hyperactivity, muscle spasm, stupor, seizures, and coma. • CV: Tachycardia, hypotension, fever, ventricular dysrhythmias. • Respiratory: Respiratory distress. • GU: Acute renal failure. • Metabolic: Metabolic acidosis, hypocalcemia.	Known, suspected, or symptomatic monofluoroacetate exposure: Oral ethanol (96%) 40–60 mL, followed by IV ethanol (10% solution in D5W) 10 mL/kg over 1 h and 1.5 mL/kg/h for the next 6–8 h. Seizures: IV BZD, progress to barbiturates.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients; activated charcoal (oral/nasogastric) 1–2 g/kg.	

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Strychnine • Diffuse/severe muscle contractions and spasms; facial muscle spasms (i.e., risus sardonicus, "sardonic smile"), trismus, opisthotonos, abdominal muscle contractions, and tonic movements of the extremities; extensor muscles more affected than flexor muscles, contractions triggered or exacerbated by auditory, tactile, or visual stimuli; respiratory failure; metabolic acidosis, rhabdomyolysis, hyperthermia.	Symptomatic patients: • Secure airway, assist breathing and ventilation. • IV propofol 1–2.5 mg/kg and then 3–12 mg/kg/h (Peds: 2.5–3.5 mg/kg then 7.5–15 mg/kg/h) *or* IV diazepam 0.1–0.5 mg/kg; IV pentobarbital 100-200 mg (Peds: 2-4 mg/kg), general anesthesia, and neuromuscular blockade with nondepolarizing agent as necessary.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) in acutely sick patients; activated charcoal (oral/nasogastric) 1–2 g/kg.	
Sedative hypnotic General: Ataxia; nystagmus; slurred speech; CNS depression (e.g., lethargy, coma, respiratory/CV/thermoregulatory centers); apnea; hypotension; myocardial depression; hypothermia; CV	Supportive care.		

collapse; (non)cardiogenic pulmonary edema/ARDS.
Barbiturate
- Atonic gut, ileus; may progress to bowel necrosis; tense, clean, bullous skin lesions over pressure points surrounded by erythema; bullae fluid has detectable amounts of barbiturate, not pathognomonic for barbiturate poisoning.

GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal (oral/nasogastric) 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus.

Urine alkalinization (long-acting barbiturates e.g., phenobarbital) enhances elimination: IV sodium bicarbonate 1–2 mmol/kg bolus followed by sodium bicarbonate infusion (150 mmol in 1,000 mL D5W) starting at 1.5–2.0 times maintenance, titrate to maintain urinary pH >7.5; monitor urine pH hourly; potassium supplement as needed.

Extracorporeal support consideration: CV instability unresponsive to conservative measures; phenobarbital: hemoperfusion clearance 100–300 mL/min; hemodialysis clearance

Barbiturates: Suppress brain activity and isoelectric EEG not indicator of poor prognosis; prolonged coma; rhabdomyolysis.

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
Barbiturate (*continued*)		60–75 mL/min; hemodialysis especially effective with activated charcoal treatment; repeat hemodialysis/hemoperfusion if serum drug levels rebound.	
Benzodiazepine (BZD) • Slurred speech; ataxia; nystagmus; lethargy, stupor, coma; loss of deep tendon reflexes; apnea (massive overdose); rare cases of cardiac arrest, ARDS, pulmonary edema.	Inadequate spontaneous ventilation or airway protection: Endotracheal intubation and mechanical ventilation. Flumazenil diagnostic aid in coma: IV flumazenil 0.1–0.2 mg followed by 0.1–0.2 mg every minute (max 2 mg) until awake, failure to respond makes BZD unlikely cause.		Flumazenil: Half-life 1–2 h; reverses sedative/anxiolytic effects, inconsistent in reversing BZD-induced respiratory depression; precipitate abrupt BZD withdrawal syndrome; unmask epileptogenic effects of polypharmacy overdoses.

Non-BZD non-barbiturate sedative hypnotic		
Baclofen • Oral: Latent toxicity 2–6 h; unreactive pupils; CNS (mimic brainstem lesion)/respiratory/CV depression; autonomic instability; hypotonia/flaccidity, areflexia; myoclonic jerking; seizures; coma; hallucinations; hypothermia; cardiac conduction abnormalities.	Prolonged respiratory support (e.g., 3–7 d).	Overdose >200 mg may be predictive of developing delirium, coma, seizures, prolonged hospital admission.
• Intrathecal: Same as oral except latent period.	Respiratory support; empty pump reservoir and record amount; may consider IV/IM physostigmine 0.5-1.0 mg at ≤1 mg/min (Peds: 0.02 mg/kg at ≤0.5 mg/min) may repeat every 5–10 min (max 2 mg) to desired response. Reduce cerebrospinal fluid (CSF) drug burden: Withdraw 30--40 mL CSF by catheter access port/lumbar puncture, and replace equal volume NS (instructions on withdrawing CSF through the catheter access port contact Medtronic, Inc., Technical Services 800-707-0933); closely monitor for symptom recurrence;	Physostigmine: Insufficient evidence to mandate routine use. Contacts: Medtronic, Inc., Technical Services and Physician Consultants (intrathecal device manufacturer) 800-707-0933; Novartis Pharma AG, Technical Services (drug manufacturer) 888-669-6682.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
	notify patient's intrathecal baclofen therapy physician.		
Carisoprodol • See (similar to) meprobamate.	Supportive care.		Carisoprodol is metabolized to meprobamate.
Chloral hydrate • GI irritation (e.g., gastritis, perforation), CNS depression; miosis; hypothermia; hypotension; respiratory depression; paradoxical CNS excitation (pediatric); myocardial depression; ventricular dysrhythmia; pulmonary edema; delayed dermal exfoliation; renal tubular necrosis; hepatotoxicity.	Ventricular dysrhythmia: IV beta-blocker (e.g., propanolol 1 mg).	Hemodialysis consideration: Prolonged coma, persistent hypotension/dysrhythmias, CV instability; hypotension and poor clinical condition are *not* contraindications for hemodialysis; repeat session(s) for rebound in serum levels.	Chloral hydrate is radio-opaque.
Ethchlorvynol • CNS depression; prolonged coma (>1 wk); hypothermia; respiratory depression; hypotension; bradycardia, seizures; aromatic pungent odor similar to a new plastic shower curtain on victim's breath.	Supportive care.	Hemoperfusion consideration: Prolonged coma; repeated sessions for rebound in serum levels.	Ethchlorvynol: Isoelectric EEG during coma.

Gamma-hydroxybutyrate (GHB), 1,4-butanediol, gamma-butyrolactone • Coma; respiratory depression; hypothermia; bradycardia; hypotension; seizures.	Supportive care; respiratory support; maybe consider IV physostigmine 0.5-1.0 mg at ≤1 mg/min (Peds: 0.02 mg/kg at ≤0.5 mg/min), may repeat every 5–10 min (max 2 mg) to desired response.		GHB: Low quality of evidence for physostigmine use; no evidence physostigmine improves outcome; insufficient evidence to mandate routine use.
Glutethimide • Thick/tenacious bronchial secretions, fluctuating level of consciousness, seizures, profound and prolonged coma, hypotension, hypothermia, persistent acidosis; anticholinergic effects.	Supportive care.	GI decontamination consideration: (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus; late activated charcoal administration may be beneficial.	
Meprobamate • CNS and respiratory depression; hypotension; dysrhythmias; bezoar formation.	Supportive care.	GI decontamination consideration: (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not	Meprobamate is a metabolite of carisoprodol. Potential for gastric concretion formation following large ingestions.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Meprobamate (*continued*)		in patients with decreased bowel sounds/ileus. Hemodialysis consideration: Serum meprobamate >20 mg/dL. Gastroscopy consideration: Suspected bezoar (e.g., relapsing conscious level, prolonged/erratic drug absorption, persistently elevated serum drug levels); gastrotomy as indicated.	
Sympathomimetic Amphetamine • Same as cocaine; in particular anxious, (paranoid) psychosis, volatile, aggressive, life-threatening agitation, visual/tactile hallucinations.	Agitation/delirium/hallucinations: IV BZD (e.g., diazepam 5-10 mg) rapidly titrated to effect; large cumulative doses may be needed (e.g., diazepam >100 mg). Seizures, hyperthermia, hypertension, hypotension: See Cocaine.		Amphetamine complications: See Cocaine. PMA: Tachycardia, hyperthermia, coma, seizures, dysrhythmias, IVCD, hypoglycemia, hyperkalemia.

Cocaine • Sympathetic hyperactivity with CNS excitation and peripheral sympathetic stimulation (e.g., mydriasis, hypertension, tachycardia, tachypnea, pyrexia, diaphoresis, headache, anxious, psychomotor agitation, confusion, psychosis, tremor, hyperreflexia, seizures, visual/tactile hallucinations); preterminal events: bradycardia, hypotension, CV collapse. • Metabolic: Metabolic acidosis; hypokalemia, hyperglycemia.	Anxiety/psychomotor agitation: IV BZD (e.g., diazepam 5-10 mg) rapidly titrated to effect; large cumulative doses may be needed (e.g., diazepam >100 mg). Seizures: IV BZD, propofol, or barbiturate. Sinus tachycardia: IV BZD (e.g., diazepam 5-10 mg or equivalent) titrated to effect. SVT: Cardioversion if hemodynamically unstable; IV BZD (e.g., diazepam 5-10 mg or equivalent); IV diltiazem 20 mg or IV verapamil 5–10 mg; IV adenosine 6 mg or 12 mg. Ventricular dysrhythmias: Defibrillate if hemodynamically unstable; IV sodium bicarbonate 1–2 mmol/kg; IV lidocaine 1.5 mg/kg bolus followed by 2 mg/min infusion; IV BZD (e.g., diazepam 5-10 mg or equivalent). ACS: Current guidelines, IV BZD (e.g., diazepam 5-10 mg or equivalent).	Cocaine complications (acute, hours, days after use): ACS, AMI, IVCD, dysrhythmias; CVA, SAH, intracerebral hemorrhage; organ ischemia/infarction, aortic dissection, vasculitis; acute lung injury/pulmonary edema/ARDS, pneumonitis (“crack lung”), pneumothorax, pneumomediastinum; rhabdomyolysis; infections (e.g., endocarditis, hepatitis, pneumonia, epidural abscess); placentae abruptio; BADS: decreased level of consciousness, profound lethargy, similar to a prolonged postictal period, normal thought content, normal sleep postures, can be aroused to orientation.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Cocaine (*continued*)	Hypertension: Rapid control of psychomotor agitation with IV BZD; IV phentolamine 1 mg, repeat in 5 min; IV nitroglycerin or nitroprusside infusion titrated to effect. Hyperthermia: Rapid control of psychomotor agitation with IV BZD; external cooling. Pulmonary edema: IV nitroglycerin infusion titrated to blood pressure; IV furosemide 20–40 mg; IV morphine sulfate 2 mg every 5 min titrated to pain relief or respiratory status. Hypotension: IV norepinephrine or epinephrine (avoid dopamine).		

Systemic asphyxiant Carbon monoxide (CO) • Headache, dizziness; nausea and vomiting; progressive impairment of consciousness; hyperventilation; hypotension; increased muscle tone, hyperreflexia, clonus, Babinski positive; skin blistering over pressure areas; metabolic acidosis with normal oxygen tension and reduced oxygen saturation; delayed neuropsychiatric sequelae.	Known or suspected CO toxicity, severe and unexplained anion gap metabolic acidosis: • Ventilate and oxygenate patient with 100% oxygen. • HBO considerations: Unconscious any time after CO exposure, neurologic or psychiatric features (e.g., coma, seizures, focal deficits, GCS <15), pregnancy, cardiac ischemia, carboxyhemoglobin (COHgb) >20%).		Pulse oximetry reading overestimates oxyhemoglobin. COHgb: Determination of venous blood sample by co-oximeter; high levels confirm CO exposure; levels not necessarily predictive of symptoms or outcome; levels can be within a laboratory reference range if oxygen treatment before obtaining blood test.
Cyanogens e.g., cyanide (CN) • Anxiety, dizziness, palpitations, headache, weakness; pulmonary edema, respiratory failure; dysrhythmias, CV collapse; CNS dysfunction, loss of consciousness, seizures, coma; metabolic acidosis. • Nitroprusside-induced CN toxicity: Tachycardia, need for escalating nitroprusside	Known or suspected CN toxicity (e.g., occupation, fire in an enclosed space), severe and unexplainable anion gap metabolic acidosis: • Ventilate and oxygenate patient with 100% oxygen. • IV dicobalt edetate 300 mg (Peds: 10 mg/kg) over 1–5 min *if* certain of the diagnosis, particularly when patient is unconscious with deteriorating	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (See Box 96-1) soon after ingestion followed by activated charcoal 1–2 g/kg. HBO considerations: CN toxicity complicated by coincidental CO poisoning.	CN toxicity is a *clinical diagnosis*; plasma lactate ≥72 mg/dL (8 mmol/L) sensitive surrogate for whole-blood CN ≥1.0 μg/mL (39 μmol/L) and significant toxicity; death ≥3.0 μg/mL (117 μmol/L); whole-blood CN concentration for confirmation of clinical diagnosis. An abnormal percent saturation gap (difference between

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
doses to maintain blood pressure control (tachyphylaxis), metabolic acidosis with increase in serum lactate concentration, a narrowing of difference in oxygen content of arterial and venous blood, and acute unexplained CNS dysfunction.	vital signs, repeat 1–2 dose base on clinical response; adverse events include hypotension, cardiac dysrhythmias, angioedema. OR • IV hydroxocobalamin 5 g over 15 min, repeat 1–2 doses base on clinical response; transient pink discoloration of mucous membranes, skin, urine; may interfere with colorimetric determinations of serum iron, bilirubin, Cr concentration. OR • IV sodium nitrite 300 mg (10 mL of a 3% solution at 2.5–5 mL/min) (Peds: 0.2 mL/kg of a 3% solution [6 mg/kg or 6–8 mL/m^2 BSA] at 2.5–5 mL/min, max 10 mL [300 mg]) *and* IV		percent oxyhemoglobin reported by co-oximeter and percent saturation calculated by blood gas analysis) does not suggest CN poisoning. Cyanogen exposure: Thermal decomposition of polyurethane foams in furniture, contributor to mortality in smoke inhalation; latent onset (>12 h) of toxicity following acetonitrile (e.g., artificial nail removers) ingestion; prolonged or excessive therapeutic use of nitroprusside; ingestion of the cyanogenic glycoside amygdalin (vitamin B_{17}) found in kernels of fruits (e.g., almonds, apples, apricots, cherries, peaches, plums).

sodium thiosulfate 12.5 g (50 mL of a 25% solution immediately following sodium nitrite) (Peds: 1 mL/kg [250 mg/kg or 30–40 mL/m^2 BSA], max 12.5 g [50 mL]); reduce sodium nitrite dosage proportionately to Hgb concentration in patients with known anemia; repeat treatment using one-half original dose of sodium nitrite *and* sodium thiosulfate if signs of poisoning reappear.

OR

- CN antidote kit: Amyl nitrite (broken in gauze and held close to the nose and mouth of spontaneously breathing patients, or can be placed into the face mask lip or inside the resuscitation bag) should be inhaled for 30 s of each min with a fresh pearl used every 3–4 min *and* IV sodium nitrite 300 mg (10 mL of a 3% solution) over 5–20 min (Peds: based on hemoglobin [Hgb] concentration; See Caveat)

Pediatric IV sodium nitrite dosing

Hgb (g/dL)	3% Sodium nitrite (mL/kg)
7.0	0.19
8.0	0.22
9.0	0.25
10.0	0.27
11.0	0.30
12.0	0.33
13.0	0.36
14.0	0.39

Excessive methemoglobinemia resulting from nitrite or 4-DMAP: IV methylene blue 1 mg/kg (onset of action ≤30 min); repeat doses based on clinical response.

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Cyanogens e.g., cyanide (CN) (*continued*)	*and* IV sodium thiosulfate 12.5 g (50 mL of a 25% solution) (Peds: 0.41 mg/kg [1.65 mL of 25% solution/kg], max 12.5 g [50 mL]) over 10 min; repeat 1–2 doses of sodium nitrite *and* thiosulfate base on clinical response. OR • IV 4-dimethylaminophenol (4-DMAP) 3–5 mg/kg; precise extent of induced methemoglobinemia may not be predictable. When diagnosis is uncertain and patient is conscious, administer IV sodium thiosulfate. Preventive nitroprusside toxicity: Add 1 g (10 mL of 10%) sodium thiosulfate to each 100 mg bag of sodium nitroprusside (i.e., 10:1 ratio).		

Hydrogen sulfide (HS) • Altered mental status; respiratory distress; pulmonary edema; cyanosis; seizures; coma; delayed neuropsychiatric sequelae; blackening of copper and silver coins in patient's pocket or darkening of jewelry.	Known or suspected HS toxicity (e.g., rapidly loses consciousness "knockdown," rotten egg odor, rescue from sewer or manure pit, multiple victims with sudden death syndrome, cardiac arrest in previously healthy worker at work site), severe and unexplainable anion gap metabolic acidosis: • Ventilate and oxygenate the patient with 100% oxygen. • IV sodium nitrite: See Cyanogens, Cyanide antidote kit, sodium nitrite component. • Consider HBO.	
Withdrawal syndrome Baclofen		
• Oral: Similar to ethanol (sedative hypnotic) withdrawal.	Oral: IV BZD and titrate to desired effects; administer oral/enteral baclofen (patient's prescribed dosing prior to withdrawal).	Baclofen: Muscular rigidity may progress to fatal rhabdomyolysis; oral dosing not reliable as sole treatment.
• Intrathecal: Latent onset 1–3 d; tachycardia, hypotension/labile blood pressure, hyperthermia, altered/depressed consciousness, hallucinations, muscular spasticity/rigidity, seizures, priapism.	Intrathecal: Administer baclofen (oral or enteral) ≥120 mg/d in 6–8 divided doses (safety not established <12 years of age) early in clinical course; restore intrathecal baclofen (ITB) therapy via programmed bolus through	

(continued)

TABLE 96-1 *(continued)*

Agent Target Organ Systemic Effect	Action Alert Critical Laboratory Value Clinical Intervention	Adjunct Therapy Extracorporeal Support	Caveat Complication
Baclofen (*continued*)	catheter access port, by lumbar puncture, or through externalized intrathecal catheter; IV BZD infusion titrated to effect until ITB therapy is restored. Consult physician experienced in ITB management; interrogate pump status using manufacturer's programming device, perform biplane or CT imaging of the pump/catheter system to identify problems (e.g., catheter leak, break, kink, dislodgement); depending on results, experienced physician should empty pump reservoir, refill with baclofen solution at proper concentration, and expeditiously perform system troubleshooting to determine cause of ITB therapy interruption.		
Gamma hydroxybutyrate (GHB),1,4-butanediol, gamma-butyrolactone	IV BZD titrated to sedation, normalization of vital signs and sensorium.		Pentobarbital may be more effective than BZDs at controlling delirium in patients with

• Withdrawal syndrome may progresses over 2–3 d; insomnia, tremor, vomiting, tachycardia, hypertension, tremor, diaphoresis, auditory/visual hallucinations, anxiety, confusion, disorientation, delirium, agitation, rapid fluctuations in sensorium, seizures.	Severe withdrawal (delirium or autonomic instability) or high-dose BZD (e.g., cumulative lorazepam dose 0.4–1 mg/kg during a 6-h period) does not control agitation and tachycardia: IV pentobarbital 1–2 mg/kg every 30–60 min titrated to sedation, normalization of vital signs and sensorium.	abnormal vital signs, paranoid delusions, and hallucinations; premature pentobarbital tapering may result in recrudescence of delirium.
Opioid • Mydriasis, lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, anxiety, restlessness; tachycardia, hypertension, myalgias, vomiting, diarrhea, anorexia, abdominal pain, dehydration; intense drug craving; not life threatening (i.e., do not have altered mental status, hyperthermia, seizures) except neonatal withdrawal and may involve seizures.	Clinical opioid withdrawal: IM methadone 10 mg, repeat in 1 h if no significant relief *or* oral clonidine 0.1–0.2 mg every 4–6 h × 5–10 d and slowly tapered by 0.2 mg/d.	IM methadone 10–20 mg will block most physiologic manifestations of withdrawal; 20–40 mg daily or divided every 12 h may be required to avoid psychologic withdrawal; after acute medical illness is stabilized, heroin-dependent patients may be tapered with methadone over 1 wk; methadone-dependent patients require ≥4 wk of gradually decreasing dosages. Clonidine: Hypotension especially with first dose; tachyphylaxis to antiwithdrawal effects may develop by 10–14 d. Complications: Dehydration, electrolyte disturbances,

(continued)

TABLE 96-1 *(continued)*

Agent **Target Organ** **Systemic Effect**	**Action Alert** **Critical Laboratory Value** **Clinical Intervention**	**Adjunct Therapy** **Extracorporeal Support**	**Caveat** **Complication**
Opioid (*continued*)			hyperthermia, rhabdomyolysis, seizures, aspiration); withdrawal treatment (e.g., CNS/respiratory depression, aspiration); underlying illness (e.g., infection, nutritional deficiencies, trauma).
Sedative hypnotics (e.g., ethanol, BZD, barbiturate, non-BZD non–barbiturate sedative hypnotic) • Tremors, vomiting, anorexia, anxiety, and insomnia, seizures (status epilepticus rare), delirium tremens (i.e., altered sensorium with pathologic autonomic and CNS hyperactivity; e.g., tachycardia, hypertension, hyperpyrexia, diaphoresis, mydriasis, disorientation, global confusion, hallucinations, delusions, mumbling speech, psychomotor agitation).	Determine need for sedation using the CIWA scale (a numbered grading system based on mental status e.g., reported anxiety, hallucinations, disorientation); goal is to control agitation: IV diazepam every 5–10 min until patient quietly sleeping, yet easily awaken, start with 5 mg (2.5 mg/min); if not effective, repeat dose; if second dose not effective, administer 10 mg for the third and fourth doses; if not effective, administer 20 mg for the fifth and subsequent doses until sedation is achieved; administer 5–20 mg every hour as needed to maintain light somnolence; may require >1 g in		Anticipate/recognize early withdrawal to allow timely treatment and prevent serious manifestations (e.g., seizures, hyperthermia, delirium); long-acting BZD with active metabolites (e.g., diazepam, chlordiazepoxide) offer prolonged therapeutic effect without need for frequent dosing; risk of respiratory depression with barbiturates; phenothiazines (e.g., prochlorperazine, chlorpromazine) and butyrophenones (e.g., haloperidol) lower seizure threshold, induce hypotension, impair thermoregulation; taper drug

	24 h or IV lorazepam 1–4 mg every 5–15 min or IM lorazepam, 1–40 mg every 30–60 min until calm, and then every hour as needed to maintain light somnolence. If unresponsive to BZD, IV propofol 1–2.5 mg/kg stat and then 3–12 mg/kg/h *or* pentobarbital 1–2 mg/kg every 30–60 min. Neuroleptic agents may be considered *in conjunction with BZD* when agitation, perceptual disturbances, or disturbed thinking not adequately controlled; IV/IM haloperidol 0.5–5 mg every 30–60 min *or* oral haloperidol 0.5–5 mg every 4 h as needed for severe agitation.	dose over 2–4 wk by 10%–20% every 3 d.

4MP, 4-methylpyrazole (fomepizole); ACLS, Advance Cardiac Life Support; ACS, acute coronary syndrome; AMI, acute myocardial infarction; APL, acute promyelocytic leukemia; ARDS, adult respiratory distress syndrome; AST/ALT, aspartate aminotransferase or alanine aminotransferase; BADS, biogenic amines depletion syndrome; BAL, dimercaprol, 2,3-dimercapto-1-propanol, British anti-Lewisite; BSA, body surface area; BZD, benzodiazepine; C, Celsius; CaEDTA, calcium disodium edetate; CAVH, continuous arteriovenous hemodiafiltration; CIWA, Clinical Institute Withdrawal Assessment; CNS, central nervous system; CPR, cardiopulmonary resuscitation; Cr, creatinine; CT, computed tomography; CV, cardiovascular; CVA, cerebrovascular accident; CVVH, continuous venovenous hemodiafiltration; d, day; DMSA, 2,3-dimercaptosuccinic acid; D5W, dextrose 5% water; DKA, diabetic ketoacidosis; ECG, electrocardiogram; EEG, electroencephalogram; FHF, fulminant hepatic failure; GCS, Glasgow Coma Scale; GFR, glomerular filtration rate; GI, gastrointestinal; GU, genitourinary; h, hours; HBO, hyperbaric oxygen; HEENT, head, ears, eyes, nose, throat; ICH, intracranial hemorrhage; ICU, intensive care unit; IM, intramuscular; INR, international normalized ratio; IV, intravenous; max, maximum; IVCD, intraventricular conduction delay; MPPP, methyl-phenyl-propionoxypiperidine; ms, milliseconds; NAC, *N*-acetylcysteine; NDI, nephrogenic diabetes insipidus; NS, normal saline; NSAIDs, non-steroidal anti-inflammatory drugs; OLT, orthotopic liver transplant; Peds, Pediatrics; PEG, polyethylene glycol (solution); PMA, paramethoxyamphetamine; PT, prothrombin time; QTc, corrected QT interval; RaVR, terminal R wave in lead aVR; R/SaVR, R-wave/S-wave ratio in lead aVR; SAH, subarachnoid hemorrhage; SC, subcutaneous; SIADH, syndrome of inappropriate antidiuretic hormone; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; SVT, supraventricular tachycardia; WBI, whole bowel irrigation; wk, weeks.

Box 96-1. Gastric lavage

Endotracheal or nasotracheal intubation should precede gastric lavage in the comatose patient; place oral airway between teeth; place patient in left lateral/head down position (20-degree tilt); measure and mark length of tube (mouth to stomach) with rounded end that is sufficiently firm to be passed into the stomach via the mouth, yet flexible enough not to cause mucosal damage (adult: at least 36–40 French [external diameter12–13.3 mm], Peds: at least 24–28 French gauge [external diameter 7.8–9.3 mm]); lubricate tube with a hydroxyethylcellulose jelly and pass the tube without excessive force; check tube placement either by air insufflation while listening over the stomach and/or, by aspiration with pH testing of the aspirate; lavage is carried out using 200–300-mL aliquots of warm fluid (e.g., normal saline, tap water), Peds: warm normal saline 10 mL/kg; volume of lavage fluid returned should approximate amount administered; continue lavage until recovered lavage solution is clear of particulate matter.

A negative or poor lavage return does not rule out a significant ingestion.

Box 96-2. Whole bowel irrigation

Insert nasogastric/oral tube and administer PEG solution at 2 L/h for 5 h, and clear rectal effluent is evident (small children: 500 mL/h); doubtful patients would be cooperative or tolerate oral PEG.

Box 96-3. Digoxin-specific antibody fragments dosing calculator

$$\text{Number of vials} = \frac{\text{Digoxin body burden to be neutralized in ng / mL (nmol / L} \times 1.28) \times \text{Weight (kg)} \times \text{Volume of distribution } (V_d)}{1{,}000 \times 0.6 \text{ mg / vial}}$$

V_d: Adults 8 L/kg, children 2–10 y 13 L/kg, infants 2–24 mo 16 L/kg, neonates 10 L/kg

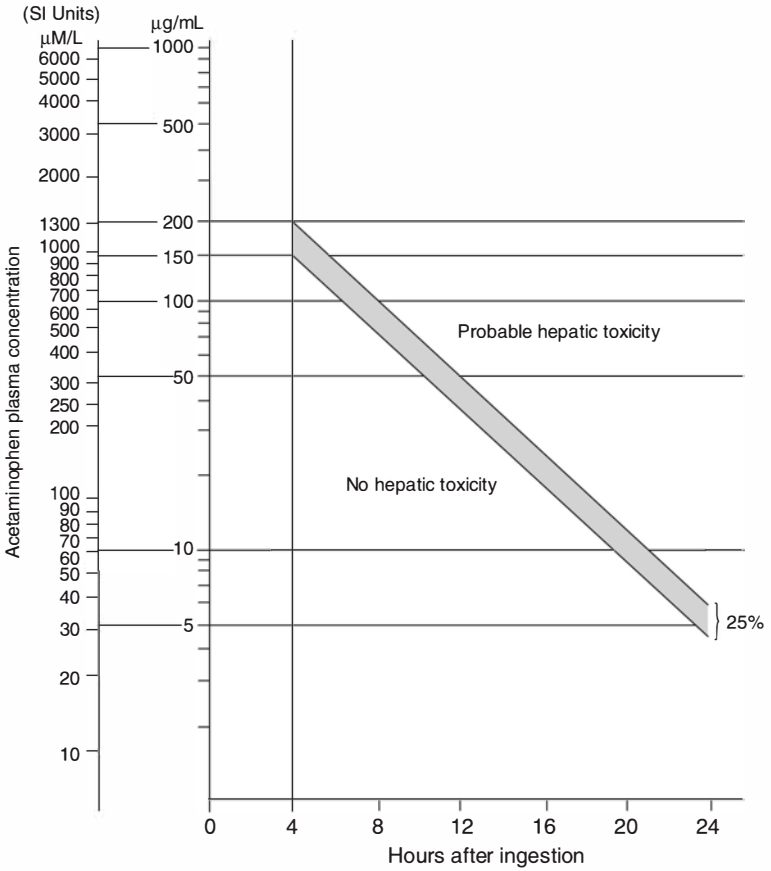

Figure 96-1. Acetaminophen toxicity nomogram.

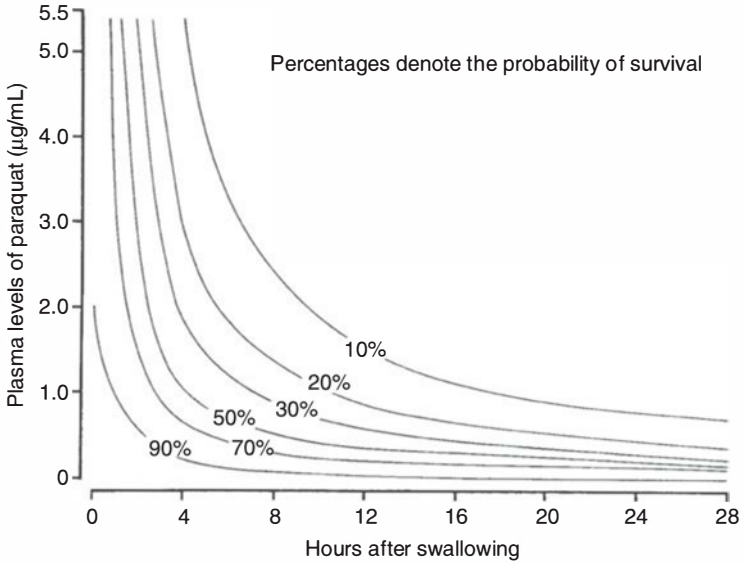

Figure 96-2. Probability survival curves in paraquat poisoning. (From Hart TB, Nevitt A, Whitehead A. A new statistical approach to the prognostic significance of plasma paraquat concentrations. *Lancet* 1984;2:1222–1223.)

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SECTION 11

Surgical Problems in the Intensive Care Unit

Fred A. Luchette

97

Epistaxis

Cynthia E. Weber, Sewit Amde, and Fred A. Luchette

I. GENERAL PRINCIPLES

A. Epistaxis is a common clinical problem that is usually mild and self-limited. However, epistaxis can become a severe and life-threatening emergency especially in the elderly.

B. Understanding the anatomy of the blood supply to the nose is essential.

1. The nose, like the rest of the face, has an abundant blood supply and may be principally divided into the following:

a. Branches from the internal carotid artery, namely the branches of the anterior and posterior ethmoid arteries from the ophthalmic artery.

b. Branches from the external carotid artery, namely branches from the maxillary artery (sphenopalatine and greater palatine arteries) and the facial artery (superior labial and angular arteries).

2. Internally, the lateral nasal wall is supplied posteroinferiorly by the sphenopalatine artery and superiorly by the anterior and posterior ethmoid arteries.

3. The nasal septum also derives its blood supply from the sphenopalatine and the anterior and posterior ethmoid arteries with the added contribution of the superior labial artery (anteriorly) and the greater palatine artery (posteriorly).

4. The Kiesselbach plexus (also called Little area) represents a region of the anteroinferior third of the cartilaginous nasal septum. It is an anastomotic network of vessels from the external and internal carotid arteries.

5. Anterior bleeding is most common and usually originates from Kiesselbach plexus.
6. Posterior bleeding usually originates from the sphenopalatine artery, is more common in the elderly, and is often more difficult to control.

II. ETIOLOGY

A. Direct trauma to nasal mucosa is the most common cause of epistaxis.

1. Digital trauma (nose picking).
2. Nasogastric and feeding tube placement.
3. Nasotracheal intubation.
4. Blunt trauma (look for associated nasal fractures).

B. Primary and secondary coagulopathies are important considerations.

1. Nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants.
2. von Willebrand disease.
3. Hemophilia.
4. Leukemia.
5. Liver disease.
6. Idiopathic thrombocytopenic purpura.
7. Vascular abnormalities, including Osler-Weber-Rendu syndrome.

C. Other factors that may increase risk of epistaxis:

1. Hypertension.
2. Deviated septum or bony deformity.
3. Rhinitis, upper respiratory infections, irritants.
4. Dry air/unhumidified oxygen (dries nasal mucosa).
5. Overuse of decongestants/sprays and cocaine use desiccate mucosa.
6. Nasal mass lesions.

III. DIAGNOSIS

A. Perform a thorough history and physical examination of the nasal cavity with speculum/rigid scope, suction, with adequate lighting.

1. Anterior versus posterior bleed should be established to allow appropriate management.

B. Imaging is rarely indicated, unless a tumor is suspected.

C. Ascertain the extent of bleeding (number of towels soaked), and check the blood count when large-volume blood loss is suspected.

D. Remember that epistaxis in a supine ICU patient with diminished awareness may present as bleeding from the oral cavity.

IV. TREATMENT

A. Most epistaxis is self-limited.

1. Usually ceases with digital pressure for 10 minutes. Have patient sit with head tilted forward to prevent airway obstruction and nausea from blood flowing into the stomach.

2. If this pressure maneuver fails, topical vasoconstrictors (epinephrine, phenylephrine, or oxymetazoline), chemical (silver nitrate) or electrocautery, and nasal packing may be necessary. Care must be taken not to perforate the septum.
3. Clear view of bleeding site is necessary for the use of a cautery method.
4. Adequately anesthetize the nose before packing or cauterizing.
   a. Anterior packing: various self-expanding/inflatable devices exist with or without vasoconstrictive agents.
   b. Posterior packing: patients may need to be sedated for standard posterior packing with rolled gauze. Foley catheter can be passed to nasopharynx, inflated, and then retracted to wedge balloon snugly in posterior choana.
   c. Packs can be left in place for 2 to 5 days; however, prophylactic antibiotics covering *Staphylococcus aureus* species should be given due to risk or sinusitis and toxic shock syndrome if left for >24 hours. Be aware of the risk of pressure necrosis.

B. In cases of severe or uncontrolled epistaxis:

1. ABCs—airway, breathing, circulation.
   a. Intubation may be necessary.
   b. Insure adequate venous access for fluid resuscitation.
2. Monitor vital signs, check blood count, type/screen, and coagulation studies.
3. Consider gastric decompression to minimize aspiration of blood.
4. Obtain consultation from an otolaryngologist.

C. If epistaxis is recurrent or refractory to packing, open or endoscopic arterial ligation or selective angiographic embolization may be necessary.

1. Anterior nasal bleeding is abated by ligation of the anterior ethmoid artery.
2. Posterior bleeding is controlled by ligation of the sphenopalatine artery.

D. Other methods that might work—cold water irrigation, have patient suck on ice cube, cold towel to forehead.

E. For patient in the intensive care setting, prevention is important.

1. Rotate and inspect nasal tubes regularly.
2. Use lubricating agents when inserting tubes.
3. Humidified oxygen is essential to prevent mucosal drying and desiccation.
4. Hypertension and coagulopathies should be treated immediately.

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98 Esophageal Perforation and Acute Mediastinitis

Cynthia E. Weber, Fred A. Luchette, and Robert M. Mentzer Jr

I. ESOPHAGEAL PERFORATION

A. Definitions. Esophageal perforation can be a result of multiple pathophysiologic etiologies.

1. "Spontaneous" perforation due to increased wall tension.
2. Penetrating injuries.
   a. Due to intraluminal pathology.
   b. Result of extraluminal causes.

B. Etiology.

1. Spontaneous (barogenic) perforation.
   a. Rapid increase in intraluminal pressure (violent vomiting—Boerhaave syndrome, blunt trauma).
   b. Necrosis of the esophageal wall from esophageal cancer.
   c. Inflammatory esophageal lesions: tuberculosis, Barrett esophagus, idiopathic eosinophilic esophagitis.
2. Extraluminal perforation.
   a. Penetrating trauma from stab or gunshot wounds.
   b. Esophageal surgery: resection or esophagomyotomy.
   c. Adjacent surgical procedures: cervical procedures, truncal vagotomy, pneumonectomy, laparoscopic Nissen fundoplication, aortic surgery, atrial fibrillation procedures through surgical or percutaneous approach, hiatal hernia repair, thoracic aneurysm repair, tracheostomy, and tube thoracostomy.
3. Intraluminal perforation.
   a. Instrumentation.
      i. More common with rigid than flexible endoscopy.
      ii. More common during interventions such as balloon dilation of a stricture.
      iii. Leading edge of a stricture is the point most likely to rupture.
   b. Esophageal stent placement, especially in the setting of prior radiation or chemotherapy.
   c. Congenital anomalies (esophageal atresia) or from nasogastric (NG) tube placement.
   d. Transesophageal echocardiography—very rare.
   e. Endotracheal intubation.
   f. Ingested foreign bodies.

g. Chemical burns from alkali or strong acids, resulting in mucosal damage and stricture.
h. Reflux esophagitis with ulceration.
i. Endoscopic sclerotherapy, laser therapy, photodynamic therapy.

C. Clinical presentation.

1. Tachycardia—earliest sign of mediastinitis.
2. Tachypnea.
3. Subcutaneous emphysema of the face and chest.
4. Pain: precordial, substernal, epigastric, or scapular due to diaphragmatic irritation.
5. Fever.
6. Dysphagia and odynophagia.
7. Hoarseness and cervical tenderness in cervical esophageal perforations.

D. Diagnosis.

1. Chest radiography (CXR): mediastinal air, hydropneumothorax, pleural effusion, subcutaneous emphysema.
2. Contrast esophagram—most sensitive diagnostic test; water-soluble contrast preferred; can confirm with barium if needed.
3. Computed tomography (CT) scan: extraluminal air, periesophageal fluid, wall thickening, extraluminal contrast.
4. Possible role for endoscopy to aid in diagnosis.

E. Treatment.

1. Early (<24 hours from the time of perforation).
   a. Primary closure with wide drainage of the mediastinum.
   b. Reinforcement of the repair with a flap of parietal pleura, intercostal muscle flap, or an omental patch.
2. Late (>24 hours or extensive inflammation).
   a. Esophageal diversion.
   b. Generous drainage.
   c. Broad-spectrum antibiotics.
   d. If small, closure over T-tube.
3. Contained perforation with no signs of sepsis: antibiotics, NG drainage, total parenteral nutrition (TPN).
4. Persistent esophagomediastinal fistula: control with esophageal stents or fibrin glue.
5. Endoscopic management—clipping, transesophageal drainage, stents alone or in combination with open or laparoscopic repair.
6. Endoluminal stenting effective for malignant perforations, especially in nonoperative esophageal cancer.

III. ACUTE MEDIASTINITIS

A. Etiology.

1. Primary mediastinitis—rare, alone or in conjunction with pharyngitis, epiglottitis, pneumonia, pericarditis, bronchitis.
2. Secondary mediastinitis—most commonly associated with sternotomy and intrathoracic or endoscopic procedures.

3. Predisposing factors for mediastinitis following cardiac surgery include advanced age, obesity, smoking, emergency surgery, lower preoperative ejective fraction, prolonged cardiopulmonary bypass time, postoperative bleeding and need for reoperation, diabetes mellitus, use of bilateral internal mammary artery grafts, immunosuppression as seen in heart transplant recipients, and use of blood transfusions.
4. Other less common causes of secondary mediastinitis:
   a. Cervical or thoracic esophageal perforation.
   b. Complications from central lines.
   c. Ludwig angina or retropharyngeal abscesses.
   d. Periodontal infections.
   e. Descending necrotizing infections.
   f. Extracorporeal membrane oxygenation (ECMO).

B. Clinical presentation.

1. Fever.
2. Pain localized to the chest or radiating to the neck.
3. Tachycardia.
4. Subcutaneous emphysema.
5. Leukocytosis.
6. Postoperative infection.
   a. Occurs 3 days to 4 weeks after surgery.
   b. Associated with sternal drainage and sternal instability.

C. Diagnosis.

1. CXR: air tracking in the mediastinum, retrosternally, or between the leaves of the sternum.
2. CT scan: localized mediastinal fluid, pneumomediastinum, pleural effusion, sternal changes; however, they may be difficult to distinguish postoperative changes from surgical dissection.

D. Treatment.

1. True acute mediastinitis is a surgical emergency.
2. Obtain blood and mediastinal fluid cultures.
3. Broad-spectrum antibiotics and source control.
4. Resuscitate to maintain adequate cardiac output and oxygen delivery.
5. Drain or debride fluid collections or necrotic tissue.
6. Open-window thoracotomy for bronchopleural or esophagopleural fistulas.
7. Irrigation and sternal debridement with rewiring for early exploration.
8. Irrigation catheter in cases of gross purulence.
9. Unilateral or bilateral pectoralis major, omental, or rectus abdominal muscle flap closure after radical sternal debridement for postoperative infections.
10. Vacuum-assisted closure (VAC) therapy for drainage, closure, and increased blood supply to the area.

E. Complications.

1. Late failure of internal mammary artery bypass grafts in postoperative mediastinitis.
2. Free right ventricular wall rupture with sternal mobilization during delayed closure or upon spontaneous cough or movement.

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99 Diagnosis and Management of Intra-Abdominal Sepsis

Yee Wong, Mary M. Wolfe, and Fred A. Luchette

I. GENERAL PRINCIPLES

A. Intra-abdominal infections are commonly encountered in the intensive care unit (ICU).

B. The presentation and causes are varied.

1. Many of these patients have undergone abdominal surgery or a procedure, and there is a suspicion for an intra-abdominal abscess.
2. Some patients will present with clinical manifestations suggestive of sepsis, but an infectious source may not be immediately evident. Radiologic imaging is helpful in these cases.
   - **a.** Causes of sepsis may be unrelated to the initial surgical procedure.
   - **b.** It may be seen in bowel ischemia, necrotizing pancreatitis, cholecystitis, or in diverticulitis.

II. ETIOLOGY

A. Pathogenesis may be secondary to spontaneous causes or to contamination of the peritoneal cavity after a perforated viscus that causes breakdown of peritoneal defense mechanisms.

B. Peritoneal defense mechanisms provide a system for effective clearance of foreign particulates and organisms from the intraperitoneal space.

1. Resident peritoneal macrophages, neutrophils, and monocytes ingest microorganisms and secrete proinflammatory cytokines.
2. Lymphatic channels provide drainage of peritoneal fluid with bacteria and proinflammatory mediators into the venous system.
3. Inspiration, especially during positive-pressure ventilation, causes a pressure gradient favoring fluid movement out of the abdomen.
4. Entry of proinflammatory cytokines into the vascular space leads to systemic sepsis and subsequent hemodynamic and respiratory changes.

C. Pathogens include mixed flora—aerobic, anaerobic, and facultative gram-negative organisms are common pathogens.

1. Facultative and aerobic gram-negative organisms release endotoxin and endotoxin-associated proteins—most notably lipopolysaccharide from their outer membrane, which triggers an intense inflammatory response.

2. Cytokines and leukocyte-derived inflammatory mediators give rise to systemic responses that can include tachycardia, fever, peripheral vasodilatation, hypotension, and decreased cardiac output.
3. Host immune defenses can be suppressed by bacterial synergy that inhibits complement activation and leukocyte migration.

III. DIAGNOSIS

A. The initial therapeutic goal should focus on resuscitation, diagnosis, and source control of the infection.

B. History, physical examination, and imaging studies are crucial to the diagnosis of intra-abdominal sepsis in the critically ill patient.

1. Systemic inflammatory response syndrome (SIRS) is defined as having two or more of the following:
   a. Temperature >38°C or <36°C.
   b. Heart rate >90 beats per minute.
   c. Respiratory rate >20 per minute or pCO_2 <32.
   d. White blood cell count >12,000 cells/mm^3 or fewer than 4,000 cells/mm^3, or with more than 10% immature (bands) forms.
2. Sepsis is defined as SIRS with an identifiable or suspected infectious source.
3. Signs and symptoms of intra-abdominal sepsis include fever, tachycardia, localized or diffuse abdominal tenderness, peritonitis, tachypnea, and delirium.
4. Laboratory findings often show leukocytosis, electrolyte abnormalities, hyperglycemia, increased liver enzymes, and elevated lactic acid.

C. Radiology.

1. Plain radiographs may reveal the following findings for intra-abdominal sepsis, but are often nonspecific.
   a. Perforation/pneumoperitoneum.
   b. Bowel obstruction.
   c. Pneumatosis intestinalis and portal venous gas from ischemic bowel.
   d. Pneumonia.
   e. Pleural effusion.
2. Ultrasound (US) may be diagnostic if an intra-abdominal abscess and cholecystitis (or nephrolithiasis) are suspected.
   a. It is noninvasive and can be done at bedside to localize extraluminal fluid collection.
   b. It can allow guided drainage of an intra-abdominal collection and biliary or ureteral drainage.
   c. Results are highly operator dependent and limited by body habitus, bowel gas, and location of abscess.
3. Computed tomography (CT) is often the most utilized diagnostic tool for intra-abdominal infection.
   a. It provides noninvasive identification of pathology not identified on physical examination, plain radiographs, or US.
   b. It may also be used for guided drainage of fluid collection.
   c. It is also helpful in diagnosing pancreatitis, colitis, and ischemic bowel.

IV. TREATMENT

A. Initial resuscitation.

1. Aggressive fluid resuscitation to counter vasodilation should be initiated before surgical or radiologic intervention in order to maintain end-organ perfusion.
2. Appropriate monitoring should be utilized, including arterial catheterization for continuous blood pressure assessment, central venous pressure, and urine output to guide the adequacy of fluid resuscitation.
3. Metabolic acidosis and coagulopathy should be corrected as expeditiously as possible.
4. Vasopressors, such as dopamine, phenylephrine, norepinephrine, and vasopressin, can also be used to increase cardiac output or reverse vasodilation. However, vasopressors should not replace volume resuscitation to maintain blood pressure and organ perfusion.

B. Administration of empiric antibiotics should be instituted as soon as intra-abdominal sepsis is suspected (Table 99-1).

1. Appropriate coverage must anticipate pathogens most likely to be encountered at the site of infection. Initial empiric antibiotics should cover enteric gram-negative facultative and obligate anaerobic bacilli or *Clostridium difficile*.
2. Proximal small bowel has gram-positive aerobic and gram-negative anaerobic organisms that are generally susceptible to β-lactam antibiotics.
3. Distal small bowel and colon perforations cause contamination with gram-negative facultative organisms and obligate anaerobes that should be covered with broad-spectrum antibiotics, such as carbapenems, cephalosporins, or penicillins plus β-lactamase inhibitors.
4. Once culture results return, empiric antibiotics should be narrowed down to target specific organisms.

TABLE 99-1 Bacteria Commonly Encountered in Intra-Abdominal Infections

Facultative gram-negative bacilli	Obligate anaerobes	Facultative gram-positive cocci
Escherichia coli	*Bacteroides fragilis*	Enterococci
Klebsiella species	*Bacteroides* species	*Staphylococcus* species
Proteus species	*Fusobacterium* species	*Streptococcus* species
Morganella morganii	*Clostridium* species	
Other enteric gram-negative bacilli	*Peptococcus* species	
Aerobic gram-negative bacilli	*Peptostreptococcus* species	
Pseudomonas aeruginosa	*Lactobacillus* species	

C. Percutaneous drainage can be performed when fluid collection is identified and when there are no signs of peritonitis. It is preferred over open surgical intervention, which is associated with increased morbidity and mortality. If the abscess is accessible by US or CT, a drain should be emergently placed and left until the abscess has resolved.

D. Surgery is indicated for evidence of intestinal perforation and diffuse peritonitis. Primary goal of surgical intervention is to control the source of contamination.

1. Bowel resections should be performed in cases of ischemic bowel, with end ostomy if necessary. When the patient is hemodynamically unstable, the bowel should be left in discontinuity (damage control) and a second-look laparotomy planned.
2. Primary closure of the wound is controversial and must take into consideration the abdominal wall edema and aggressiveness of the volume resuscitation required, in order to avoid abdominal compartment syndrome.
   a. A temporary abdominal closure device, such as vacuum-assisted abdominal dressing, has been gaining popularity in recent years. It allows for rapid application and easy reentry into the peritoneal cavity, and avoids abdominal compartment syndrome.
   b. Temporary closure also shortens the time when the patient is under anesthesia. Resuscitation and correction of acidosis and coagulopathy can then be completed in the ICU until the patient is hemodynamically stable before definitive closure of the abdomen.
   c. Second-look laparotomy may also be necessary to achieve complete control of infection.

V. SPECIFIC INFECTIONS

A. Acute pancreatitis.

1. Infections superimposed on acute pancreatitis are among the most difficult intra-abdominal infections to manage.
2. See Chapter 100.

B. Biliary infections.

1. Ascending cholangitis is often caused by biliary obstruction with secondary bacterial infection of the bile, and patients can present with Charcot triad; right upper quadrant (RUQ) abdominal pain, fever, and jaundice. With severe disease and development of sepsis, patients may also have mental status changes and hypotension in addition to the triad, also known as the Reynold pentad.
   a. US or CT may show biliary ductal dilatation with gallstones or with inflammatory changes when acalculous cholecystitis is present.
   b. Laboratory findings include hyperbilirubinemia, leukocytosis, and elevated liver enzymes.
   c. Treatment includes resuscitation, broad-spectrum antibiotics, and supportive care. If there is no clinical improvement in 24 to 48 hours, one should proceed with drainage of the common bile duct with endoscopic retrograde cholangiopancreatography/percutaneous or

transhepatic cholangiography (ERCP/PTC). ERCP or PTC should not be delayed for imaging if cholangitis has been diagnosed based on clinical presentation and laboratory findings.

d. Initial antibiotic therapy should be monotherapy with a β-lactam/β-lactamase inhibitor or metronidazole with third-generation cephalosporin or a fluoroquinolone.

2. Acute cholecystitis.

a. Acalculous cholecystitis is most common in ICU secondary to microvascular and mucosal dysfunction and presents as occult sepsis with or without RUQ tenderness.

b. US/CT may show gallbladder wall thickening, pericholecystic fluid, and sludge.

c. Treatment includes antibiotics and percutaneous cholecystostomy tube for high-risk patients who are not a surgical candidate for cholecystectomy and do not respond to antibiotic therapy.

d. Initial antibiotic therapy is the same as the treatment for ascending cholangitis.

C. Mesenteric ischemia (see Chapter 101).

1. Arterial or venous occlusion or low flow states are causative factors. Thromboembolic events should be considered in the setting of atrial fibrillation or arrhythmia.

2. Plain radiographs can be used to evaluate for pneumatosis intestinalis and portal venous gas in cases of severe ischemia, but are often inconclusive.

3. Angiography is considered the gold standard for diagnosing mesenteric ischemia; however, it is invasive and should be delayed if patient presents with peritonitis.

4. CT is useful to evaluate stable patients with less specific symptomatology. Early changes such as bowel dilatation and transmural thickening with inflammatory changes in the perienteric fat can sometimes be seen.

D. Postoperative intra-abdominal infections.

1. It must be considered in patients with signs of sepsis who have undergone gastrointestinal (GI) anastomosis or those who present with peritonitis.

2. Patients with anastomotic leak will often develop fever, tachycardia, and leukocytosis during the early postoperative period. Management usually involves relaparotomy with abdominal washout, resection of the anastomosis, and creation of an end ostomy.

a. Percutaneous drainage can be considered if an abscess adjacent to an anastomosis is small and easily accessible by CT, and the patient is clinically stable.

b. Antibiotic therapy should target specific enteric pathogens and then be tailored to final sensitivities.

E. Enteric fistulas.

1. About 15% to 25% of mortality associated with enteric fistulas is secondary to sepsis and multiorgan system failure.

2. Small intestine is the most common source, followed by the colon, stomach, duodenum, biliary tract, and pancreas.

3. Multiple risk factors inhibit the spontaneous closure of fistulas, including foreign bodies, radiation, inflammatory bowel diseases or infection, epithelialization or fistula tract <2 cm in length, neoplasm, and distal obstruction.
4. The patient typically presents with sepsis, increased drainage from wound, electrolyte abnormalities, and malnutrition.
5. Management includes adequate fluid resuscitation, drainage of the infection, control of fistula output, nutritional support with total parenteral nutrition if necessary for high-output fistulas, skin and wound care, and definitive closure of fistula.

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100 Acute Pancreatitis

Jennifer K. Plichta and Fred A. Luchette

I. DEFINITIONS

A. Clinically acute pancreatitis: Rapid onset of pain associated with alterations in exocrine function and inflammatory changes of the pancreas on imaging studies.

B. Clinically chronic pancreatitis: Repeated episodes of pain associated with diminished exocrine function.

C. Functionally acute pancreatitis: The pancreas was and will be functionally normal before and after the attack.

D. Functionally chronic pancreatitis: The pancreas was functionally abnormal before the attack and may remain abnormal after the attack.

E. Pathologically acute pancreatitis.

1. Mild: predominant tissue changes are inflammatory, with interstitial edema, intrapancreatic or peripancreatic disruption, and associated fat stranding.
2. Severe: predominant tissue changes are necrotic, associated with focal or diffuse acinar cell necrosis, thrombosis of intrapancreatic vessels, intraparenchymal hemorrhage, and areas of liquefaction.

F. Pathologically chronic pancreatitis: associated with scarring, fibrosis, calcification, and atrophy of acinar tissue.

II. ETIOLOGY

A. Chronic alcohol use.

1. Associated with a mean ethanol consumption of 150 to 175 g/day for 18 years for men and 11 years for women before the first attack.
2. Mechanism for resulting acute or chronic pancreatitis is not clear, although likely multifactorial.

B. Gallstone disease.

1. Along with chronic alcohol use, it accounts for 60% to 80% of patients with acute pancreatitis.
2. Three theories of gallstone pancreatitis:
   - **a.** "Common channel"—stones lodge at the ampulla of Vater with a common biliopancreatic channel proximal to the stone-induced obstruction resulting in bile refluxing into the pancreatic duct, triggering pancreatitis.
   - **b.** "Duodenal reflux"—an incompetent sphincter of Oddi due to stone passage permits reflux of duodenal juice containing activated digestive enzymes into the pancreatic duct.

c. "Pancreatic duct obstruction"—the only theory currently supported by clinical models; after duct obstruction, lysosomal hydrolases activate digestive enzymes within pancreatic acinar cells, leading to their injury.

C. Drugs.

1. Most commonly seen in patients with immune system abnormalities.
   a. Acquired immunodeficiency syndrome (AIDS) patients receiving dideoxyinosine or pentamidine.
   b. Transplant or inflammatory bowel disease (IBD) patients receiving azathioprine or mesalazine.
2. Diuretics (thiazides, ethacrynic acid, and furosemide), sulfonamides, and simvastatin also have an association with pancreatitis.

D. Pancreatic duct obstruction.

1. Tumors: duodenal, ampullary, biliary tract, or pancreatic.
2. Inflammatory lesions: peptic ulcer, duodenal Crohn disease, and periampullary diverticulitis.
3. Developmental abnormalities: pancreas divisum and Sphincter of Oddi dysfunction.
4. Other structural abnormalities: choledochocele, pancreatic cysts or pseudocysts, periampullary diverticula, and ductal strictures.
5. Infections: mumps, coxsackievirus, *Mycoplasma pneumoniae*, ascariasis, and *Clonorchis.*

E. Miscellaneous causes of acute pancreatitis.

1. Post-procedural: duct exploration, sphincteroplasty, distal gastrectomy, endoscopic retrograde cholangiopancreatography (ERCP), which has been shown to be decreased by the administration of rectal indomethacin, and procedures associated with hypoperfusion or atheroembolism of the pancreatic circulation.
2. Abdominal trauma.
3. Pregnancy.
4. Hereditary (i.e., mutations in PRSS1, SPINK1, CFTR/cystic fibrosis).
5. Hypercalcemia and hypertriglyceridemia.
6. Idiopathic pancreatitis: affects 5% to 10% of population, and possible etiologies include biliary sludge and autoimmune mechanisms.

III. CLINICAL PRESENTATION

A. Symptoms: epigastric pain of rapid onset, pain radiating to the back (often band-like), nausea, vomiting that may result in Mallory-Weiss syndrome, diarrhea, loss of appetite, and fever/chills.

B. Physical examination.

1. Tachycardia, tachypnea, diaphoresis, hyperthermia, delirium, and jaundice (20% incidence).
2. Abdominal tenderness with voluntary or involuntary guarding, rebound, distension, epigastric mass, and diminished or absent bowel sounds.
3. Hemorrhagic complications can produce flank ecchymoses (Grey-Turner sign) or other evidence of retroperitoneal bleeding (Cullen sign, hemorrhagic discoloration of the umbilicus).

IV. DIAGNOSIS

A. Serum lipase.

1. Increases 4 to 8 hours following the onset of symptoms.
2. Normalizes within 7 to 14 days after the treatment.
3. More sensitive and specific than serum amylase.

B. Serum amylase.

1. May be normal in 10% of patients with lethal pancreatitis.
2. Levels increase 2 to 12 hours after attack onset and normalize within 3 to 6 days.
3. May be elevated due to other processes: acute cholecystitis, perforated gastric or duodenal ulcers, bowel obstruction, or salivary gland disease.

C. Routine blood tests.

1. Increased hemoglobin, hematocrit (HCT), blood urea nitrogen (BUN), creatinine, bilirubin, white blood cells (WBCs), glucose, and triglycerides.
2. Decreased calcium, albumin.
3. Severe cases may result in thrombocytopenia, decreased fibrinogen levels, prolonged prothrombin time, and partial thromboplastin time.
4. Other laboratory tests to consider: liver function tests and arterial blood gas analysis.

D. Routine radiography.

1. Chest radiograph: left pleural effusion, basal atelectasis.
2. Plain frontal supine radiograph of the abdomen: pancreatic calcifications in chronic pancreatitis, ileus, and retroperitoneal air if pancreatic abscess is formed.

E. Ultrasonography: detection of cholelithiasis, bile duct dilatation, or both.

F. Computed tomography (CT).

1. Mild pancreatitis—normal or slightly swollen pancreas with streaking of retroperitoneal or transverse mesocolic fat.
2. Severe pancreatitis—peripancreatic or intrapancreatic fluid collections, areas of pancreatic necrosis fail to enhance with contrast administration, and intrapancreatic air suggests pancreatic necrosis or abscess.

G. Differential diagnosis: perforated hollow viscus, cholecystitis/cholangitis, bowel obstruction, mesenteric ischemia/infarction, or peptic ulcer (consider posterior perforation into the pancreatic bed).

V. PROGNOSIS

A. Mild, self-limited in 90% to 95% of patients.

B. Approximately, 5% to 10% of patients will have a severe attack that is associated with 40% morbidity and mortality.

C. Ranson prognostic signs.

1. *On admission*: age > 55 years; WBC > 16,000/mm^3; glucose > 200 mg/dL; lactate dehydrogenase (LDH) > 350 international units/L; glutamic-oxaloacetic transaminase (GOT) > 250 units/dL.

2. *During initial 48 hours*: HCT decrease >10%; BUN rise >5 mg/dL; serum calcium <8 mg/dL; Pao_2 < 60 mm Hg; base deficit > 4 mEq/L; and fluid sequestration >6 L.
3. Less than three criteria: mild pancreatitis—1% mortality.
4. Seven or eight criteria: severe pancreatitis—90% mortality.

D. APACHE-IV—a method for more precisely determining mortality risk.

E. Peripancreatic fluid collections on CT scan.

1. Two or more fluid collections—61% incidence of late pancreatic abscess.
2. One fluid collection—12% to 17% incidence of pancreatic abscess.
3. Pancreatic enlargement only—zero incidence of pancreatic abscess.

VI. TREATMENT OF ACUTE PANCREATITIS

A. The main goal of initial management is to maintain adequate organ perfusion that typically consists of adequate isotonic volume administration, analgesia, antiemetics, and continual reassessment of clinical parameters.

B. Analgesia: hydromorphone may be preferred over morphine, as morphine stimulates the sphincter of Oddi to contract.

C. Fluid and electrolyte replacement (isotonic crystalloid preferred over colloid).

1. Initially, hypochloremic alkalosis due to vomiting and decreased fluid intake.
2. Subsequently, metabolic acidosis due to hypovolemia, poor tissue perfusion, and management with chloride-containing fluids.
3. Hypomagnesemia and hypoalbuminemia due to preexisting malnutrition in chronic alcoholism.
4. Untreated hypocalcemia may lead to tetany and carpopedal spasm.
5. Hemodynamic alterations of severe attacks resemble septic shock: increased heart rate, cardiac output, cardiac index, arterial–venous oxygen difference and decreased pulmonary vascular resistance and hypoxemia.

D. Other treatments.

1. Unclear value of nasogastric suction and agents that reduce pancreatic function, inhibit inflammatory or cytotoxic responses, or inhibit digestive enzymes.
2. Use of early enteral nutrition (initiated within 36 hours of symptom onset) has shown benefit over parenteral nutrition in terms of duration of hospital stay, infectious morbidity, and need for surgery.
3. Consider foley catheter and/or central venous catheter.

E. Role of surgery and endoscopy for gallstone pancreatitis.

1. Mild pancreatitis—no indication for early surgical or endoscopic intervention.
2. Severe gallstone pancreatitis—early surgical or endoscopic intervention should be considered to either remove the source of the gallstones (i.e., cholecystectomy) or to relieve a possible obstruction from choledocholithiasis (i.e., ERCP with sphincterotomy and possible stent placement).
3. Recurrent attacks of gallstone pancreatitis may be prevented by cholecystectomy combined with surgical or endoscopic duct clearance.

VII. PREVENTION AND TREATMENT OF SYSTEMIC COMPLICATIONS

A. Aggressive fluid and electrolyte therapy may be the most effective method of preventing pulmonary and renal failure.

B. Pulmonary toilet and monitoring of pulmonary function with arterial blood gas measurements should be considered.

C. Prophylaxis with antacids, H_2-blockers, or proton-pump inhibitors (PPIs) may prevent stress-induced bleeding of gastroduodenal lesions, although this remains controversial.

D. For most patients with acute pancreatitis, antibiotic prophylaxis does not reduce the risk of infectious complications and is associated with an increased risk of death.

1. Intravenous imipenem or meropenem for 14 days may be of benefit in patients with infected pancreatitis by reducing mortality and morbidity.
2. Fluconazole decreases the emergence of resistant fungi.

E. All patients are at increased risk for thrombotic complications and require venous thromboembolism prophylaxis.

VIII. LOCAL COMPLICATIONS OF PANCREATITIS

A. Definitions.

1. Acute pancreatic and peripancreatic fluid collections—pancreatic inflammation results in fluid collections (lacking walls) and often occur early, in or near the pancreas.
2. Pancreatic necrosis—either sterile or infected area of nonviable pancreatic tissue, diffuse or focal, associated with peripancreatic fat necrosis.
3. Pancreatic pseudocyst.
   a. Occurs 4 to 6 weeks after the acute episode, nonepithelialized wall of fibrous or granulation tissue enclosing a collection of pancreatic juice rich in digestive enzymes.
   b. Leakage into peritoneal cavity or chest leads to pancreatic ascites or pancreatic–pleural fistula, respectively.
4. Pancreatic abscess—circumscribed intra-abdominal collection of purulence with gas close to the pancreas with or without necrosis.

B. Diagnosis.

1. Contrast-enhanced CT—identifies and quantitates areas of pancreatic necrosis or abscess based on extraintestinal gas, poor enhancement, or Gram stain of CT-guided fine-needle aspirate.
2. ERCP—determines communication of fluid collections with the main pancreatic duct and/or localizes the point of duct rupture.

C. Management.

1. Acute fluid collections—resolve spontaneously and rarely require treatment.
2. Sterile pancreatic necrosis—typically nonoperative management, unless clinically deteriorates despite aggressive nonoperative treatment.
3. Infected pancreatic necrosis—surgery is considered the gold standard, although current guidelines suggest waiting until the 3rd or 4th week after the onset of symptoms in the stable patient.

4. Pancreatic abscess—percutaneous or surgical drainage is recommended.
5. A step-up approach using percutaneous drainage followed by minimally invasive video-assisted retroperitoneal debridement (VARD) and peroral endoscopic necrosectomy have been shown to be superior to traditional open necrosectomy.
6. Pseudocysts—treat only if symptomatic, regardless of size, with internal surgical drainage (cystogastrostomy, cystoduodenostomy, and Roux-en-Y cystojejunostomy), endoscopic drainage (cystogastrostomy and cystoduodenostomy), or percutaneous drainage with or without administration of somatostatin.
7. Pancreatic ascites or pancreatic–pleural fistula—bowel rest, nutrition, somatostatin; most require ERCP for identification of ductal disruption with subsequent distal pancreatectomy, Roux-en-Y pancreatojejunostomy, or endoscopic stent placement.

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101 Mesenteric Ischemia

Yee Wong and Peter E. Rice

I. GENERAL PRINCIPLES

A. Defined as a compromise of intestinal arterial or venous perfusion that may occur acutely or over the course of several months in the setting of chronic ischemia.

B. Decreased blood flow and oxygen to the bowel leads to ischemia, acidosis, leukocytosis, and the eventual development of sepsis and multiple-organ failure.

C. Mortality is in excess of 60% to 80% for acute arterial occlusion, usually due to a delay in diagnosis and the rapid progression of intestinal ischemia to tissue necrosis.

D. Risk factors include advanced age, atrial arrhythmias, history of congestive heart failure or recent myocardial infarct, valvular heart disease, previous cardiac or vascular surgeries, and atherosclerotic disease.

E. Early diagnosis and prompt revascularization are the key factors to a favorable outcome.

II. ETIOLOGY

A. Acute mesenteric ischemia is usually divided into three categories, with occlusive disease or thromboembolism accounting for 80% of all cases.

1. Mesenteric arterial occlusion from embolism, thrombosis, dissection, vasculitis, or stent placement.
2. Mesenteric venous occlusion secondary to bowel obstruction, thrombosis, or phlebitis.
3. Nonocclusive ischemia as a result of cardiopulmonary bypass, various shock states, and vasoconstrictive medications (i.e., α-adrenergic, digitalis, or vasopressin).

B. Mesenteric arterial embolism or thrombosis involves the superior mesenteric artery (SMA) in 85% of cases. Most individuals have preocclusive atherosclerotic disease in other locations, including the visceral vessels.

C. Emboli from a cardiac source typically lodge at the first branch point of the SMA, the inferior pancreatoduodenal artery. Arterioarterial emboli tend to be smaller and lodge in the more distal mesenteric circulation.

D. Thrombosis usually develops at or near the origin of vessels or areas of concurrent atherosclerotic stenoses. In contrast with embolic occlusion, acute ischemia from thrombosis is usually a late complication of atherosclerotic disease and develops after two of the three mesenteric arteries are completely occluded.

E. Mesenteric venous thrombosis (MVT) is a rare disorder resulting from a variety of acquired and inherited hypercoagulable states. MVT usually involves the superior mesenteric and splenic veins and, less commonly, the inferior mesenteric and portal veins.

III. PATHOPHYSIOLOGY

A. Acute arterial obstruction will rarely present with acute mesenteric ischemia at normotensive pressures due to the excellent collateral circulation of the gut.

B. Ischemic times as short as 3 hours can produce significant irreversible damage to the intestinal mucosa.

C. Reduction of blood flow initiates a cascade of events, including an acute inflammatory response with the release of cytokines and platelet-activating factor, resulting in the breakdown of the mucosal barrier with bacterial translocation and the ultimate progression of sepsis, multisystem-organ failure, and death.

D. Nonocclusive ischemia is the result of mesenteric vasospasm, usually in the distribution of the SMA.

1. Homeostatic mechanisms attempt to maintain cardiac and cerebral perfusion at the expense of visceral and peripheral organs.

IV. DIAGNOSIS

A. Clinical presentation.

1. One hallmark of acute mesenteric ischemic is pain out of proportion to the physical examination.
2. Onset of pain may be accompanied by gut emptying (e.g., vomiting, bowel movement, or diarrhea).
3. Bloody bowel movements and tachycardia are also common late signs of intestinal ischemia.
4. Physical examination may reveal diffuse abdominal tenderness, hypoactive to absent bowel sounds, and peritoneal findings with progression of disease to bowel infarction and perforation.
5. A high index of suspicion in patients with preexisting cardiac disease and critically ill patients with a shock state from trauma, burns, and sepsis.
6. Patients with acute ischemia from thrombosis may have a history of chronic postprandial abdominal pain associated with significant weight loss.

B. Laboratory findings.

1. Elevation of serum amylase concentration.
2. Elevation of serum lactate often implies severe ischemia or bowel infarction.
3. Most common laboratory abnormality is a persistent and profound leukocytosis; in excess of 15,000 cells/mm^3.
4. Electrolyte derangements from dehydration and acidosis with pH < 7.2 and base deficit of 7 to 8 are seen in the advanced stages of intestinal infarction.

C. Imaging.

1. Plain radiographs typically demonstrate no abnormalities until late in the clinical course. Late findings include distended bowel loops with air-fluid levels, bowel wall thickening, intestinal pneumatosis, which is very specific for bowel necrosis, portal venous gas, and free air from perforation.
2. Duplex ultrasonography is highly specific; however, the result is highly operator dependent and can be limited by distended bowel loops or in obese patients.
3. Computed tomography (CT) is also highly specific and is usually the imaging study of choice for rapid diagnosis. Computed tomographic angiography has a sensitivity of 96% and specificity of 94% in diagnosing acute mesenteric ischemia. It is usually preferred over conventional angiography for its noninvasiveness and ability to evaluate for other abdominal pathologies. Findings for ischemia include bowel wall thickening and/or distention, mesenteric fat stranding, pneumatosis, and portal venous gas.
4. Angiography remains the "gold standard" for imaging of mesenteric occlusion and can even be diagnostic for nonocclusive disease. It can also offer therapeutic interventions; however, it is invasive and is limited to patients without peritoneal signs.

V. TREATMENT

A. Acute mesenteric ischemia is a vascular emergency, and immediate surgical intervention improves outcome. Emergent laparotomy is usually indicated when patients present with signs of peritonitis.

B. Aggressive resuscitation is essential as patients will likely develop systemic inflammatory response with progression of ischemia.

C. SMA embolism.

1. Arteriotomy with embolectomy should be performed as soon as possible. Closure of arteriotomy can be achieved primarily or with patch angioplasty.
2. Bowel resection should be performed after revascularization when frank bowel necrosis is present. Second-look laparotomy within 48 hours is warranted when reperfusion injury is suspected.
3. Endovascular approaches with thrombolysis, angioplasty, and stenting are alternative options for high-risk patients without signs of bowel infarction or in the setting of chronic mesenteric ischemia.

D. SMA thrombosis.

1. In patients with extensive stenosis, an antegrade or retrograde bypass with prosthetic or autologous venous grafts is required. Antegrade aortomesenteric bypass has been the procedure of choice historically. However, retrograde iliomesenteric bypass has also been described, although there is no convincing evidence that one approach is superior to the other. Venous graft is usually preferred in patients with bowel infarction.

2. Endovascular stenting with or without thrombolysis may be beneficial for chronic mesenteric ischemia with extensive collateral circulation; however, it is limited to patients without signs of bowel compromise.

E. Nonocclusive ischemia.

1. Expedient management of cardiac events and shock states is essential. Systemic vasoconstrictors should be avoided and replaced by vasodilators that diminish cardiac preload and afterload when possible.
2. Pharmacologic treatment may involve selective intra-arterial infusion of papaverine into the SMA.
3. If peritoneal signs develop or abdominal pain persists despite papaverine infusion, emergent exploratory laparotomy is indicated.

F. Mesenteric venous thrombosis.

1. Conservative management with bowel rest and systemic anticoagulation (heparin followed by warfarin).
2. Percutaneous endovascular intervention with direct thrombolysis into the superior mesenteric vein (SMV) or portal vein may be indicated if systemic anticoagulation is ineffective.
3. Laparotomy is usually reserved for complications, such as bowel infarction. Management involves bowel resection and venous thrombectomy if thrombosis is localized to SMV or portal vein.

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102 Compartment Syndrome of the Abdominal Cavity

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I. GENERAL PRINCIPLES

A. Overview.

1. The abdominal cavity is considered as single compartment enclosed by an aponeurotic envelope with limited compliance.
2. First coined by Kron et al. in 1984 when they described the pathophysiologic changes following a ruptured abdominal aortic aneurysm.
3. Elevated intra-abdominal pressure (IAP) can impair blood flow and organ function.
4. Once critical threshold volume is reached, small increments in tissue volume lead to exponential increases in intraperitoneal pressure. Elevated IAP may result in multiorgan failure and death if not reversed promptly.

B. Definitions.

1. Compartment syndrome: increased pressure in a confined anatomic space that adversely affects function and viability of tissue within the compartment.
2. Abdominal compartment syndrome (ACS): acutely increased and sustained pressure within the abdominal wall, pelvis, diaphragm, and retroperitoneum, adversely affecting function of organs and tissue within and adjacent to the abdominal cavity. Usually requires operative decompression of the peritoneal cavity.
3. Intra-abdominal hypertension (IAH): sustained (>6 hours) increase in IAP that may or may not require operative decompression.
4. On the basis of the consensus statement of the World Society of the Abdominal Compartment Syndrome, IAH was defined as IAP ≥ 12 mm Hg and ACS as a sustained IAP ≥ 20 (measured at the level of the mid-axillary line), which is associated with new organ dysfunction or failure. Note that there is no definitive IAP at which ACS occurs.
   a. Normal abdominal pressure: 10 mm Hg.
   b. Grade I: 12 to 15 mm Hg.
   c. Grade II: 16 to 20 mm Hg.
   d. Grade III: 21 to 25 mm Hg.
   e. Grade IV: >25 mm Hg.

TABLE 102-1 Causes of Abdominal Hypertension

Peritonitis, trauma, burns	Retroperitoneal hematoma
Fluid overload: hemorrhage or septic shock	Peritoneal operative trauma
Bowel edema, reperfusion injury, acute pancreatitis	Ileus, bowel obstruction
Intra-abdominal mass	Abdominal closure under tension
Ascites, intra-abdominal fluid collection	Laparoscopic abdominal insufflation
	Weight lifting up to >200 mm Hg (physiologic abd. hypertension)

II. PATHOPHYSIOLOGY

A. Causes: Most IAH is caused by peritoneal, mesenteric, or retroperitoneal edema impinging on the fascial envelope of the abdominal compartment.

1. Total surface area of peritoneum is about 1.8 m^2, which is approximately equal to the entire surface area of skin. Theoretically, 1 mL of peritoneal thickening may contain 15 to 18 L of fluid.
2. Expanding edema can quickly exceed compensatory elasticity of abdominal fascia and diaphragm and can lead to organ function compromise.
3. Increased venous outflow resistance results in reduction in effective perfusion of the capillary beds, leading to tissue ischemia and inflammatory mediator activation.

B. Table 102-1 lists many of the causes of IAP.

III. DIAGNOSIS

A. Clinical presentation.

1. The key to diagnosis includes identifying patients at risk, recognizing salient clinical features, and remaining proactive in carrying out diagnostic measures to confirm the diagnosis.
2. Patients typically present with a tense abdominal wall, shallow respirations, low urinary output, and increased central venous pressure.
3. Physiological impairments in all systems observed.
   a. Cardiac: Output initially rises as a result of increased venous return from intra-abdominal veins but diminishes as pressure rises above 10 mm Hg.
      i. Decreased preload, result of pooling in lower extremities and functional narrowing of the vena cava.
      ii. Afterload increased and ventricular function decreased as filling pressures were negatively affected by increased IAP.
   b. Pulmonary: Decrease in diaphragmatic excursion resulting in atelectasis, and ventilation–perfusion mismatch. Positive end-expiratory ventilation to maintain alveolar patency worsens intrathoracic pressure and cardiac output.

c. Renal: Impaired as a result of decreased cardiac output, compression of both renal inflow and outflow, and direct compression of kidney parenchyma; development of "renal compartment syndrome."
d. Hepatic: Reduction in blood flow affecting production of acute-phase proteins, immunoglobulin, and factors of the other host defense system.
e. Gastrointestinal (GI): Splanchnic hypoperfusion possibly affecting mucosal pH, bacterial translocation, and bowel motility.

B. Measurement of IAP.

1. Direct method: Intraperitoneal catheter is connected to a pressure transducer to take direct measurements. This is the preferred method for most experimental studies.
2. Indirect method: Less invasive; relies on pressure transduction to the inferior vena cava, stomach, or, most commonly, the bladder. Transvesical technique: bladder behaves as passive diaphragm when volume is low; abdominal pressure can be measured transvesically.
   a. Instill no more than 25 mL of sterile saline into the empty bladder through Foley catheter. Tubing drain clamped and 18-gauge needle advanced through aspiration port and connected to pressure transducer or manometer.
   b. Recordings correlated with direct measurements in range of 5 to 70 mm Hg.

IV. TREATMENT

A. Conservative and nonsurgical measures.

1. The best treatment for ACS is prevention.
2. Early recognition of patients at increased risk prompts the institution of early corrective/preventative measures before full-blown ACS develops.
3. Nonsurgical treatment options include the following:
   a. Gastric and rectal decompression.
   b. Sedation and neuromuscular blockade.
   c. Body positioning.
   d. Diuretics, venovenous hemofiltration/ultrafiltration.
   e. Paracentesis.

B. Decompression.

1. Nonoperative decompression reserved for distension caused by ascites.
2. Operative decompression: Opening abdominal cavity in the operating room or intensive care unit once intravascular fluid deficits, temperature, and coagulation abnormalities are corrected.
   a. Postdecompression compensation has been reported: Systemic vascular resistance falls markedly after decompression, with cardiac output increases that are usually not sufficient to maintain the preintervention blood pressure.
   b. Careful monitoring, volume resuscitation before decompression, and judicious use of vasoconstrictors postoperatively are recommended.

C. Closure.

1. The abdomen can be reapproximated by a variety of methods.
2. Type of closure dependent on degree of decompression; the abdomen can be reclosed when fascia can be reapproximated without undue tension.
   a. Vacuum-assisted closure (VAC) techniques such as the commercial Wound VAC (Kinetic Concepts, San Antonio, Texas) are now widely used.
   b. Synthetic fascial materials that are sutured to the fascial edges, which can be approximated slowly, offer another reliable option (Artificial Burr, Wittmann Patch); all meshes help to decompress the abdomen, fascial reapproximation, and final closure; however, they can be difficult.

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103 Necrotizing Fasciitis and Other Soft Tissue Infections

Stewart R. Carter, David H. Ahrenholz, and Fred A. Luchette

I. OVERVIEW

A. General principles.

1. Our skin functions as a barrier to infection; therefore, any break in the skin can allow bacteria to invade.
2. Risk factors for infection include trauma, edema, hematoma, ischemia, and foreign body.
3. Virulent infections are associated with impaired host defenses (i.e., diabetes, cancer, malnutrition, immunosuppression, advanced age, and major trauma).

B. Pathophysiology.

1. Group A, β-hemolytic *Streptococcus pyogenes*: highly virulent; cellulitis; erysipelas with demarcated borders; ecthyma contagiosum; streptococcal lymphangitis; seen in necrotizing fasciitis; exotoxins result in lymphocyte activation causing shock (toxic shock syndrome [TSS]) (see Sections II and III).
2. *Staphylococcus aureus*: most common cause of skin infection; purulence; folliculitis (dermis); superficial abscess (soft tissue); carbuncle (burrowing infection); pyomyositis (hematogenous spread to intramuscular hematoma); also associated with necrotizing fasciitis. Also produces TSS (see Sections II and IV). A growing number of skin and soft tissue infections (SSTIs) are the result of methicillin-resistant *Staphylococcus aureus* (MRSA) infection.
3. *Clostridium perfringens, Clostridium novyi*, *Clostridium septicum*, and *Clostridium tertium*: most common in ischemic muscle; exotoxins cause myonecrosis and sepsis (see Section V).
4. *Eikenella corrodens*: human bite wounds; sensitive to cephalosporins and penicillin.
5. *Pasteurella multocida*: animal bites or scratches; treat with cephalosporins, penicillin, tetracycline, trimethoprim–sulfamethoxazole + clindamycin.
6. *Vibrio vulnificus*: aggressive disease; more common in alcoholics; due to immunologic defects; marine-related organisms; aggressive debridement and treat with doxycycline plus intravenous ceftazidime. Ciprofloxacin is alternative (see Section III).

7. *Escherichia coli*, *Klebsiella*: abscess of perineal area; usually arising from infected pilonidal cyst or laceration of rectal mucosa causing a perirectal abscess; can occur in other areas; initially treat with drainage and fluoroquinolones when indicated.
8. *Cryptococcus neoformans* and other fungi can mimic cellulitis due to group A *Streptococcus* (see Section II).
9. *Bartonella*: Gram-negative bacteria previously classified as rickettsiae; cause several uncommon diseases: cat-scratch disease, an acute febrile anemia, a chronic cutaneous eruption, and disseminated disease in immunocompromised hosts; treat with gentamicin and a second antibiotic depending on the *Bartonella* species and severity of the disease process.
10. Actinomycosis: chronic localized or hematogenous infection due to *Actinomyces israelii*; local abscess with multiple draining sinuses; seen more commonly in adult males as cervicofacial (lumpy jaw) abscess, portal of entry is decayed teeth; treat with surgical excision followed by cephalosporins.

II. CELLULITIS AND SUBCUTANEOUS INFECTIONS

A. Etiology.

1. Most common organisms: *S. aureus* and group A streptococci causing a diffuse cutaneous infection; nonpyogenic; starts with a minor break in skin, such as an insect bite, puncture limited to skin, and subcutaneous tissues; infections spread through tissue facilitated by toxins and enzymes.
2. In the extremity: presents with lymphadenitis or lymphangitis involving dermal lymphatics.
3. High-risk cellulitis when infection involves the face or extremities of immunocompromised patients.
4. Folliculitis: nontoxic pyodermas centered in hair follicles.
5. Subcutaneous abscess (complicated cellulitis): most common soft tissue infection.
6. Hidradenitis suppurativa: chronic burrowing infection of groin or axilla involving infected hair follicles; more commonly seen in diabetic or very obese patients.
7. Community-acquired MRSA: because of increasing cases of MRSA soft tissue infections, the distinction between community-acquired, and health care–associated MRSA is becoming less useful in guiding therapy.

B. Diagnosis.

1. Presents with progressive erythema and edema; may cause tenderness over the involved area.
2. Varying diagnostic yield on cultures of tissue or aspirate; due to the emergence of MRSA, routine culture is important for guiding antimicrobial susceptibility.

C. Treatment.

1. Uncomplicated cellulitis: treatment with antibiotics and elevation; surgery not indicated unless joints or tendon sheath are involved.
2. β-lactams (penicillins, nafcillin, cephalosporins, carbapenams), or if concern for MRSA; clindamycin, trimethoprim–sulfamethoxazole, doxycycline, minocycline, or linezolid.

3. Abscess, furuncle, or carbuncle all require incision and drainage.
4. Complicated SSTI in hospitalized patients should be treated with intravenous antibiotics with empiric coverage for MRSA pending culture results; vancomycin, linezolid, telavancin, or clindamycin.

D. Complications.

1. Symptoms refractory to medical management may indicate missed abscess or fluid collection; imaging can be helpful in determining depth of involvement.
2. Recurrent cellulitis of the upper extremities is most commonly seen after a modified radical mastectomy or axillary lymph node dissection; it is seen in the lower extremities after saphenous vein harvesting for coronary artery bypass grafting surgery; it is best treated with long-term antibiotics targeting group A *Streptococcus*.

III. NECROTIZING FASCIITIS

A. Definition.

1. A severe, progressive, and rapidly spreading infection along fascia planes with minimal cutaneous signs.
2. Typically occurs after trauma or surgery in immunocompromised patients (i.e., those with peripheral vascular disease, diabetes, or malignancy).
3. Fournier gangrene: a rapidly spreading infection of the scrotal skin.
4. Meleney gangrene: streptococcal dermal gangrene anywhere on the body.
5. Requires prompt surgical debridement and parenteral antibiotics; if not treated aggressively, necrotizing fasciitis can result in death.

B. Etiology.

1. Predisposing factors include diabetes mellitus, immune suppression, end-stage renal failure, liver cirrhosis, pulmonary diseases, malignancy, and use of injection drugs.
2. Necrotizing fasciitis (NF) has been reported after treating cellulitis with β-lactams secondary to rapid release of exotoxins.
3. Associated with hematogenous seeding of contusion after blunt trauma.
4. Infection in children is rare and is usually in the setting of *Varicella zoster* infection complicated by streptococcal skin infections.
5. Classified into three major types:
   a. Type I (80% of cases)—polymicrobial, often caused by a synergistic mixture of anaerobes, and facultative anaerobes (*E. coli*, *Pseudomonas* spp., and *Bacteroides* spp.); easily recognized clinically; associated with better prognosis.
   b. Type II (<20% of cases)—often monomicrobial, skin- or throat-derived. Group A β-haemolytic *Streptococcus* alone or with *S. aureus*; aggressive with mortality rate of 32% to 56%.
   c. Type III (rare)—gram-negative, often monomicrobial; marine-related organisms, *Vibrio* spp., that is, *V. damselae* and *V. vulnificus*.
6. NF due to fungal infection, usually follows traumatic wounds or burns; *Candida* spp. affect immunocompromised, while the *Zygometes mucor* and *Rhizopus* spp. are more common in immunocompetent; mortality >47%, highest in immunocompromised.

C. Diagnosis.

1. Pain out proportion to physical findings, edema, fever, and leukocytosis with a left shift.
2. Blistering, erythema, skin crepitus, and dermal necrosis are rare, but suggestive findings.
3. Streptococcal necrotizing fasciitis develops rapidly within 24 to 48 hours with typical symptoms plus tachycardia, localized erythema, edema, and watery drainage; positive blood cultures; blistering of skin, which turns dusky after cutaneous vascular thrombosis.
4. Diagnosis is made at time of surgical exploration. Plain radiographs or computed tomography scan may show gas fluid but often only show tissue edema. Magnetic resonance imaging with gadolinium can differentiate necrosis from inflammatory changes. If NF is suspected, surgical exploration is mandatory and should not be delayed by imaging.

D. Treatment.

1. Immediate surgical referral improves survival; surgical debridement after fluid resuscitation; preoperative antibiotics to cover for polymicrobial infection.
2. Empiric broad-spectrum antibiotic coverage with multidrug regimens, including high-dose penicillin for group A *Streptococcus*, high dose clindamycin for limiting exotoxin production, and a fluoroquinolone or aminoglycoside for gram-negative coverage. *Vibrio* spp. are treated with doxycycline plus ceftazidime or alternatively with ciprofloxacin.
3. Due to the emergence of penicillin-resistant staphylococci, a fourth-generation antistaphylococcal cephalosporin, with an aminoglycoside and metronidazole should be considered when MRSA is not a concern.
4. Modifications to the antibiotic regimen should be based on intraoperative Gram stain and wound cultures.
5. Serial debridement with daily dressing changes; vacuum-assisted closure on clean tissue to promote wound granulation.
6. Wound can then heal by secondary intention or can be skin grafted.
7. Amputation of the extremity is sometimes necessary to control the spread of infection.
8. Intravenous (IV) immunoglobulin administration can be helpful for TSS.
9. Diverting colostomy reduces perineal soiling but is not mandatory for Fournier gangrene.
10. Aggressive nutritional support: treatment is similar to burned patient (1.5 × basal metabolic expenditure).
11. Postsurgery hyperbaric oxygen (HBO) increases subcutaneous tissue oxygen tension and is generally accepted, although there is no definitive clinical data to support its use; HBO use should not delay debridement or amputation.

E. Complications.

1. Delayed diagnosis or incomplete debridement can result in profound sepsis and death.
2. Intra-abdominal sepsis can follow postoperative treatment of necrotizing fasciitis.

3. Mortality ranges from 25% to 30% with worse prognosis associated with increasing age, female gender, delay of surgical intervention, elevated serum lactate, and multisystem organ failure.

IV. NONCLOSTRIDIAL MYONECROSIS

A. Etiology. Same as necrotizing fasciitis; rarely *Aeromonas hydrophilia* or *Bacillus cereus*.

B. Diagnosis. Similar signs and symptoms of necrotizing fasciitis; radiographs show gas outlining muscles; debridement reveals muscle and fascia necrosis; differs from clostridial myonecrosis as there are mixed organisms on Gram stain and fewer systemic effects.

C. Treatment. Excision of all necrotic tissue including muscle, fascia, and skin.

D. Complications. Overall mortality is 76%.

V. CLOSTRIDIAL MYONECROSIS

A. Definition.

1. Necrotizing muscle infection often with *C. perfringens* exotoxins; requires debridement and sometimes amputation.
2. *Gas gangrene*: term describing clostridial myonecrosis; gas is seen in both clostridial abscess and nonclostridial myonecrosis.
3. Gram stain shows large number of gram-positive rods, few polymorphonuclear leukocytes (PMNs) are found in the exudates, and free fat globules are demonstrated with Sudan stain.

B. Etiology.

1. Can be traumatic or spontaneous in origin.
2. Traumatic clostridial myonecrosis is associated with war injuries, farm machinery accidents, or deep tissue wounds exposed to soil organisms. Other causes include surgical manipulation, irrigation with pressure devices, injection and air, and disruption of the esophagus or trachea.
3. Can occur when a wound is inadequately debrided; contamination from gastrointestinal or biliary tract surgery with leakage of contents into soft tissue; *C. perfringens* is the most common toxin-producing organism.
4. Spontaneous gangrene occurs in the absence of obvious bacterial entry or contamination. Presents as a primary infection of the perineum, scrotum, or extremity. Associated with *C. septicum* and *C. tertium*. Associated with colonic lesions (e.g., neoplasms) and subsequent translocation of gut flora.

C. Diagnosis.

1. Sudden onset of excruciating pain at infectious site. Rapid development of a foul-smelling wound with serosanguinous discharge and air bubbles. Woody or brawny edema gives way to cutaneous blisters with maroon-colored fluid. Necrotic tissue can advance several inches per hour with delayed treatment.
2. Severe systemic toxicities; delirium and septic shock.
3. Muscle changes from a lusterless pink to deep red then gray–green/mottled purple; muscle does not contract on stimulation.

4. Other causes of dermal necrosis: ischemic dermal necrosis (dry gangrene); ulcerating skin lesions (Meleney cutaneous gangrene); also seen in disseminated intravascular coagulation after septicemia (purpura fulminans), streptococcal necrotizing fasciitis.

D. Treatment.

1. Surgical emergency: wide debridement of nonviable fascia and muscle.
2. Wound is packed open.
3. Penicillin G 12 to 20 million units/day plus clindamycin or tetracycline. *Clostridium tertium* is highly resistant to penicillins and clindamycin and should be treated with a tetracycline, vancomycin, or metronidazole.
4. HBO therapy may be helpful particularly in extremities, as a supplement to antibiotics and surgical exploration and excision of necrotic tissue but should not delay surgical debridement.
5. Amputation of infected limb remains the single best life-saving measure.

E. Complications. Worse prognosis if hematuria is present.

VI. TOXIC SHOCK SYNDROME

A. Etiology.

1. Usually exotoxin-producing strains of *S. aureus* and *S. pyogenes.*
2. Disease progression stems from a superantigen toxin that allows the nonspecific binding of major histocompatibility complex (MHC) II with T-cell receptors, resulting in polyclonal T-cell activation.
3. *Staphylococcus aureus* commonly colonizes skin and mucous membranes in humans.
4. Associated with use of tampons in women and complications of skin abscesses or surgery.

B. Diagnosis.

1. Characterized by sudden onset of fever, chills, vomiting, diarrhea, muscle aches, and rash.
2. Diagnosis of TSS is probable with five out of six clinical criteria present and confirmed with all six; Criteria are as follows:
   a. Fever ≥38.9°C.
   b. Diffuse, macular erythrodermic rash.
   c. Desquamation, particularly on the palms and soles, can occur several weeks after onset of the illness.
   d. Hypotension.
   e. Multisystem involvement of three or more of the following:
      i. Gastrointestinal—diarrhea and emesis early in illness.
      ii. Thrombocytopenia (platelet count ≤100,000/mm^3).
      iii. Central nervous system (CNS) involvement.
      iv. Renal failure (serum creatinine greater than two times normal).
      v. Hepatic—serum total bilirubin twice the upper limit of normal.
      vi. Hyperemia of mucous membranes (oropharyngeal, vaginal or conjunctival).
   f. Negative blood culture, cerebrospinal fluid (CSF), or throat swab (blood may be positive for *S. aureus*) as well as a rise in titer to Rocky Mountain Spotted Fever, leptospirosis, or measles.

3. Diagnosis of streptococcal toxic shock-like syndrome (STSS) requires isolation of group A *Streptococcus* from a normally sterile site (e.g., blood), hypotension and two or more of the following:
   a. Renal failure (serum creatinine greater than two times normal).
   b. Hepatic inflammation (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] greater than two times normal).
   c. Thrombocytopenia (platelet count <100,000/mm^3).
   d. Desquamation, particularly on the palms and soles, can occur several weeks after onset of the illness.
   e. Soft tissue necrosis (NF, myonecrosis, or gangrene).

C. Treatment

1. Aggressive IV fluid resuscitation, targeted antibiotics, and immunomodulatory therapy with Intravenous immunoglobulin (IVIG) (1,000 mg/kg day 1 and 500 mg/kg days 2 and 3).
2. Methicillin-sensitive *S. aureus* can be treated with nafcillin, cloxacillin, or flucloxacillin, plus clindamycin; MRSA requires vancomycin, linezolid, or teicoplanin, plus clindamycin.
3. STSS treatment consists of penicillin in conjunction with clindamycin.
4. With proper treatment, patients usually recover in 2 to 3 weeks. The condition can be fatal within hours.

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104 Pressure Ulcers: Prevention and Treatment

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I. EPIDEMIOLOGY

A. In an acute care setting, the incidence of pressure sores ranges from 7% to 9% with an associated prevalence between 14% and 17%.

B. Residents in chronic care facilities, such as those with spinal cord injuries and patients in the intensive care units (ICUs), are at the highest risk for the development of pressure sores.

C. The development of pressure ulcers in the ICU results in increases in length of stay, morbidity, mortality, and associated health care costs.

II. PATHOPHYSIOLOGY

A. Pressure sores form as the end result of unrelieved pressure exerted on tissue overlying bony prominences; approximately 80% develop over the sacrum, coccyx, femoral trochanters, ischial tuberosities, lateral malleoli, and heels.

B. Normal arterial capillary blood pressure is critically low when external pressures are >32 mm Hg. Tissues overlying bony prominences are subject to this critical pressure while a patient is in the supine position.

C. Prolonged exposure to ischemia results in tissue necrosis; differing tissues exhibit different sensitivities to ischemia.

1. Muscle has much poorer tolerance to pressure than does skin or subcutaneous tissue.
2. Muscle and subcutaneous tissue infarction without skin necrosis is the "tip of the iceberg" phenomenon.
3. Studies have shown that ischemic necrosis can be prevented with intermittent restoration of blood flow.

D. Risk factors associated with pressure ulcer formation in ICU patients include tissue hypoxia, hypotension, excessive moisture or perspiration, hyper-/hypothermia, malnutrition, impaired mobility and sensation, the presence of positioning devices such as restraints, braces, vests, or fixation devices, and fecal or urinary incontinence. Unrelieved pressure associated with naso- and orogastric tubes and endotracheal tubes is also a risk factor.

III. PREVENTION

A. Prevention of pressure sores begins with education and dedicated care.

1. Institutions should have structured risk assessment policies and practice to identify vulnerable patient populations; risk assessment should be conducted on admission and repeated as necessary, particularly when acuity increases.
2. Skin assessment and routine care should be performed to identify early signs of pressure damage; avoid massaging, friction, and turning onto body surfaces with erythema from previous episodes of pressure loading.
3. Offer high-protein mixed oral nutritional supplements and/or tube feeds in addition to an appropriate diet in individuals with malnutrition and risk for pressure ulcers.
4. Repositioning should be considered in all at-risk individuals and must take into consideration the condition of the patient and support surface in use.
5. Support surfaces used for pressure redistribution; foam mattress, air mattress, low air loss beds, air-fluidized beds, and oscillating support surfaces.
6. Patients with acute traumatic injuries and a decreased level of consciousness should be removed from backboards and cervical collars as soon as safely possible; careful pressure redistribution in all surgical patients, specifically during positioning prior to, during, and after surgery.

IV. WOUND CLASSIFICATION

A. Stage I: Nonblanchable erythema of the skin with the lesion being limited to the epidermis and dermis; may be difficult to detect in individuals with dark skin tones.

B. Stage II: Partial-thickness ulceration with loss of dermis; shallow open ulcer with a viable wound bed without slough; may also present as an intact or open/ruptured blister.

C. Stage III: Full-thickness ulceration extending to the subcutaneous fat; may include undermining or tunneling.

D. Stage IV: Full-thickness tissue loss with exposed muscle, tendon, or bone; can extend into supporting structures, making osteomyelitis or osteitis likely.

V. WOUND MANAGEMENT

A. Management strategies entail identification, debridement, wound dressings, pressure dispersion, and maximization of overall health status.

1. Most stage I and II ulcers respond well to these measures.
2. Stage III and IV ulcers may require sharp or enzymatic debridement; moist dressings are recommended to provide an optimal wound environment for healing exposed tissue.
3. Data concerning the use of negative-pressure wound therapy in the management of pressure ulcers are inconclusive, although some studies have documented success.
4. An occlusive hydrocolloid dressing can be used as an alternative in a well-debrided wound with minimal dead space.
5. Deeper ulcers also respond to the use of air-fluidized pressure dispersion mattresses.
6. Optimize nutrition; supplementation of vitamin C and fish oils both have shown benefit in healing pressure ulcers.

B. With appropriate care, up to 80% of pressure sores heal without surgery.

C. Operative treatment is reserved for patients with wounds showing poor healing despite maximal conservative therapy.

1. Surgery is less frequently required in the ambulatory patient.
2. Spasticity must be medically addressed as part of treatment for pressure ulcer in spinal cord–injured patients.
3. Devitalized tissue is removed, and, if necessary, bony prominences are partially reduced.
4. A variety of musculocutaneous or fasciocutaneous advancement flaps are used to achieve closure, depending on the wound location.
5. Care is taken to avoid hematoma formation and tension on the closure.
6. Complications of flap creation include infection, wound dehiscence, skin necrosis, hematoma, seroma, and bursa formation.

D. Postoperatively, it is critical to avoid compression on the flap vascular pedicle and minimize tension or shearing forces.

1. A special air or fluid mattress is important for the first 3 weeks.
2. Gradually, a program of weight bearing is used for the following 6 to 8 weeks.
3. The greatest challenge is to minimize future risks of pressure sore development.

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105 Pain Management in the Critically Ill

Jennifer K. Plichta, Donald S. Stevens, and Fred A. Luchette

I. OVERVIEW

A. Pain, discomfort, restlessness, and agitation are major problems for critically ill patients.
B. The ideal strategy aims to manage patient pain and discomfort first, before providing sedative therapy, often resulting in improved patient outcomes.
C. Pain may be under-treated, as a result of avoiding depressing spontaneous ventilation, inducing opioid dependence, and precipitating cardiovascular instability.
D. Appropriate pain resolution facilitates recovery.
E. Pain and anxiety are difficult to measure, because they constitute subjective phenomena. The clinician should not judge the appropriateness of pain, but rather concentrate on managing it appropriately.

II. GENERAL PRINCIPLES

A. Identify the etiology of pain.
B. Determine a baseline before starting treatment, and assess the degree of pain in an objective manner with the help of validated scales and instruments.
C. Understand other potential contributing factors such as anxiety, ethnocultural factors, situational meaning, and prior experience.
D. Establish and maintain drug levels for appropriate analgesia and anxiolysis, and determine the end point of treatment.
E. Understand that therapy is an iterative process in which measurements are made, therapeutic actions are taken, effectiveness is reevaluated, and action is repeated until the desired clinical outcome is reached.

III. DEFINITIONS AND PATHOGENESIS

A. *Pain* is an unpleasant sensory and emotional experience that can be associated with actual or potential tissue damage.
B. *Pain-related behavior* is the only manifestation that can make the observer conclude that pain is being experienced.
C. *Acute pain* has an identifiable temporal and causal relationship to an injury, in contrast to *chronic pain* that persists beyond the healing process and may not have an identifiable cause.
D. *Nociception* is the detection and signaling of the presence of a noxious stimulus.

E. Pathophysiology of pain.

1. Acute pain begins with damage to the skin or other innervated tissues.
2. Locally produced and released mediators (prostaglandins, small peptides) sensitize or stimulate peripheral nociceptors, whose fibers propagate the signal into the dorsal horn of the spinal cord or the sensory nuclei in the brainstem.
3. Before reaching pain-specific areas in deep brain structures or the cortex, the signal is modulated (amplified or attenuated) that can increase or decrease the response to painful stimuli.

IV. DIAGNOSIS

A. *Location*: It should be determined whether the location is consistent with the type of injury sustained or the surgery performed, or whether it is entirely different.

1. Look for unrecognized sources of pain, such as missed or new injuries.
2. Pain can be chronic, neuropathic, or a result of malpositioning during surgery.
3. Medication selection and dosages may be influenced by a history of chronic pain, medication usage, sleep disturbance, fatigue, arthritis, alcohol or other substance abuse, and psychiatric illness.

B. *Intensity*: Visual or verbal analog scales aid in quantifying a patient's pain, thereby providing a baseline for the evaluation of the response to treatment.

1. The most widely used scale is the visual analog scale (VAS), where a spectrum of pain from "no pain" to "the worst pain I've ever had" is depicted as a scale from 0 to 10.
2. In patients who are unable to communicate (e.g., intubated), markers of sympathetic activity such as restlessness, sweating, tachycardia, lacrimation, pupillary dilation, and hypertension can be graded as signs of pain intensity.
3. It is important to identify reliable and valid tools for evaluating pain in the noncommunicative patient in the ICU. Parameters such as facial expression, upper limb movement, compliance with mechanical ventilation, among others, may be important factors that can help determine if the patient is experiencing pain.

C. *Quality of sensation*: Pain can be sharp if it is due to direct nociception (e.g., incision), dull or aching if it arises from deeper structures, or pulling or tugging in nature if it is related to the presence of sutures or visceral stimulation.

1. Pain manifested as tingling, stinging, or buzzing sensations is usually related to abnormal neural function, secondary to either recovery from regional anesthesia or reestablishment of neural function after neural compression.
2. Painful dysesthesias may occur in conjunction with peripheral neuropathy.

D. *Confounder*: Delirium.

1. A transient disorder of attention and cognition resulting in intermittent agitation, hallucinations, disruptive behavior.
2. Common in critically ill patients.
3. Identify the type and potential cause (e.g., induced by sedative or analgesic medications).

E. Assessment and reassessment.

1. Patient-focused sedation and analgesia stress the importance of individual assessment of patients and periodic reevaluation.
2. Identify all therapeutic interventions and measures that may be causing or contributing to pain-related distress (e.g., suctioning, intubation, nasogastric tubes, phlebotomy, or placement of invasive lines).

F. Monitoring the degree of sedation.

1. Successful sedation protocols.
   a. Frequently assess pain, anxiety, and agitation using a reproducible scale.
   b. Utilize combination therapies coupling opioids and sedatives.
   c. Encourage careful communication between team members.
2. Two broad categories of sedation protocols:
   a. Patient-targeted sedation protocols rely on structured assessments to carefully guide drug titrations.
   b. Daily interruptions of continuous sedative infusions may be employed to focus care providers on the goal of achieving a period of awakening in the earliest phases of critical illness possible.
3. Several numerical scales have been developed to help guide the appropriate dosage of analgesic/sedative medication based on the depth of sedation.
   a. The most popular is the 6-point Ramsay Scale (RS)—based on motor responsiveness, ranging from 1 = anxious or restless or both, to 6 = no response to stimulus; demonstrates excellent interrater reliability.
   b. Other scales include the Sedation–Agitation Scale (SAS), Richmond Agitation–Sedation Scale (RASS), Glasgow Coma Scale (GCS), and the Motor Activity Assessment Scale.
4. More sophisticated monitoring techniques currently being used in the operating room, like the bispectral index (BIS), provide objective data based on cortical and subcortical interactions, are still being investigated.

V. TREATMENT

A. *Peripheral analgesia*: nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetic infiltration, and peripheral nerve blockade.

1. NSAIDs—achieve analgesia through nonselective, competitive inhibition of cyclooxygenase (COX), thereby interfering with the production of prostaglandins and other mediators of the inflammatory cascade.
2. Ketorolac—shown to provide additional analgesia when used in conjunction with opioid analgesics without compromising respiratory drive.
   a. Adverse effects: nausea, peptic ulceration, and inhibition of platelet function.

b. Severe bronchospasm can occur in patients with asthma, nasal polyposis, or an allergy to NSAIDs.
c. Contraindicated in acute or chronic renal failure and in the presence of hypovolemia; should not be given for >5 days; renal function should always be monitored.

3. Local infiltration with anesthetics.
a. Useful in the management of postoperative pain.
b. Analgesic effect persists for at least 48 hours.
c. Prolonged effect is termed *preemptive analgesia*, and was shown to be superior to spinal or general anesthesia in the control of postoperative pain after hernia repair.

4. Repeated intermittent intercostal nerve blocks have been used to provide analgesia for thoracic injuries and surgery.
a. Nerve blocks provide analgesia without sedation or respiratory depression.
b. The need for repeated injections, the risk for pneumothorax, and the risk for systemic toxicity are disadvantages of this procedure.

5. Paravertebral nerve blockade provides analgesia over several dermatomes by bathing multiple intercostal nerves with an anesthetic via a single injection or continuous infusion through a catheter.

6. Intrapleural analgesia with bupivacaine is useful for analgesia in the thorax and upper abdomen.
a. Unfortunately, this technique loses effectiveness in the presence of a thoracostomy tube (anesthetic is drained out of the pleural space) or if the pain is bilateral (increased absorption and toxicity, and bilateral sympathetic blockade).
b. Contraindications to this technique include fibrosis of the pleura, inflammation/infection with or without blood or fluid in the pleural space, and anticoagulation or infection at the site of injection.

7. Other regional blocks include brachial plexus blocks and femoral nerve or lumbar plexus blocks for the upper and lower extremities.

B. *Spinal cord analgesia:* transcutaneous electrical nerve stimulation (TENS) and epidural and intrathecal infusions of local anesthetics or opioids.

1. TENS utilizes high frequency (80 to 100 Hz), low-intensity stimulation through sterile skin electrodes, in combination with other methods of analgesia.
a. Down-modulates the afferent nociceptive signal at the spinal cord and brainstem levels, thereby controlling postoperative (peri-incisional) pain.
b. Associated with reduced rates of complications (nausea, vomiting, atelectasis, ileus).

2. Afferent conduction can be blocked at the nerve root or spinal cord level with local anesthetics; nociceptive signals can be centrally down-modulated by intraspinal opioids acting on specific opioid receptors in the dorsal horn.

3. Regional analgesic techniques include subarachnoid and epidural administration of local anesthetics, opioids, or mixtures thereof, with intermittent dosing or continuous infusion.

a. Continuous subarachnoid analgesia with local anesthetics can be used to manage postoperative pain. It requires continuous bedside monitoring because of the potential for profound sympathectomy and hemodynamic instability. It has been associated with central nervous system infection, but current techniques are safe for at least 48 hours.
b. Continuous epidural infusion of local anesthetics allows for prolonged analgesia, although frequently associated with hypotension due to sympathetic blockade. This side effect can usually be managed with intravascular volume expansion or small doses of an α-adrenergic agent.
c. The opioid most commonly used for epidural blockade is morphine, which, because of its low lipid solubility, tends to stay dissolved in the cerebrospinal fluid. Systemic absorption and rostral spread may be responsible for adverse effects such as nausea, pruritus, urinary retention, and respiratory depression (usually preceded by progressive sedation rather than decreased respiratory rate). Naloxone can be used to treat significant respiratory depression. Epidural catheters usually remain in place for at least 2 to 3 days; may remain in place indefinitely, as long as there are no signs of infection or inflammation. Combinations of local anesthetics with opioids for continuous epidural infusion often result in fewer side effects and increased effectiveness in postoperative pain management.

C. Inhalational anesthetic agents have a limited role in critically ill patients.
1. Useful during short, painful procedures such as dressing changes in burn patients.
2. Complications may result from prolonged exposure, such as toxicity and bone marrow suppression.

D. Sedatives (such as benzodiazepines, barbiturates, phenothiazines, and butyrophenones) are given in conjunction with opioids and are used for anxiolysis, sedation, and production of amnesia.
1. Potential for depressing consciousness and respiratory effort.
2. Useful in patients who need prolonged mechanical ventilation or require sedation for the first 24 to 48 hours postoperatively.

VI. DOSING

A. Systemic opioid analgesia.
1. Limited use in ICU patients due to extreme delay in attaining therapeutic levels.
2. Typically given as IV, IM, or SC injections; small IV doses are most effective.
3. An alternative is the use of a transdermal fentanyl patch.
a. They have various rates of delivery and have a delayed onset of action of 12 to 16 hours.
b. Potential complications arise from choosing the wrong dose, particularly in opioid-naïve patients.
c. Side effects may gradually worsen and persist longer than expected, depending on skin blood flow.

B. Continuous IV infusion of opioids is a relatively simple technique, as long as the loading dose and the rate of infusion are calculated correctly to maintain therapeutic levels.

1. Most opioids have a half-life of 3 hours.
2. The dose required to maintain a level of analgesia is one-half the loading dose used to achieve analgesia in the first place.
3. This maintenance dose is divided by 3 to calculate the hourly requirements.
4. When patients experience breakthrough pain, it must be addressed as new-onset pain and the new infusion rate titrated to effect.

C. Patient-controlled analgesia (PCA) administers small doses of an opioid IV on a demand basis.

1. When establishing the upper limit for PCA (1- to 4-hour dosage limit), a temporary fivefold increase in need during the early postoperative period must be considered, from what was originally calculated for an hourly requirement.
2. Maintenance doses should generally not exceed 0.02 mg of morphine per kg, or 1.5 mg per dose in most adults.
3. The lockout interval (5 to 10 minutes) accounts for the time required for an adequate concentration of the opioid to be established at the active site before another dose is given.
4. PCA is useful for maintaining established analgesia but not for establishing it in the first place.
5. Most patients actually choose not to eliminate pain entirely.
6. Overdose with PCA is rare because patients tend to titrate themselves into the therapeutic range. Overdose is a significant risk if a basal infusion rate is administered.
7. Accumulation tends to occur if the rate is set too high.
8. Basal rates should not exceed half the estimated hourly requirement.
9. Lack of adequate analgesia results from inadequate dosing secondary to the patient failing to understand the technique, equipment malfunction, or programming errors.
10. An unusual problem is parent- or spouse-controlled PCA.
11. PCA requires that patients are awake and cooperative.
12. PCA has also been used to give epidural medications (patient-controlled epidural analgesia [PCEA]) with considerable safety and efficacy.

VII. SELECTION OF DRUGS

A. Analgesics.

1. Morphine.
   - **a.** First-line opioid recommended for use in the ICU.
   - **b.** Hydrophilic, delayed peak affect; causes histamine release, venodilation, and a decrease in heart rate.
   - **c.** Significant dosing variability related to tolerance and metabolic and excretory ability.
   - **d.** Adverse effects include respiratory depression, nausea, ileus/constipation, spasm, pruritus, and contraction of the sphincter of Oddi.

e. Renal impairment may cause accumulation of morphine-6-glucuronide (a potent analgesic with 20 to 40 times the activity of morphine), making it a suboptimal analgesic in critically ill patients.

2. Fentanyl.
   a. Good choice for patients with hemodynamic instability or in patients with morphine allergy.
   b. 80 to 100 times more potent than morphine and has a short duration of action when administered in small doses.
   c. Fat-soluble, synthetic opioid undergoes hepatic metabolism.
   d. Continuous infusions may lead to accumulation and prolonged drug effects.
3. Remifentanil.
   a. Fat-soluble, short-acting opioid.
   b. Metabolized by nonspecific blood and tissue esterases and undergoes rapid metabolism; independent of the duration of infusion or any organ insufficiency.
   c. Can be used for analgesia and sedation in all kinds of adult ICU patients.
   d. Results in rapid and predictable offset of effect, with subsequent reduction in weaning and extubation times.
4. Hydromorphone.
   a. Approximately 5 to 10 times more potent than morphine.
   b. Minimal hemodynamic effects.
5. Methadone.
   a. Synthetic opioid that can be given enterally or parenterally.
   b. Drug of choice in patients who have prolonged mechanical ventilation requirements and recovery times.
   c. Also used to wean patients off infusions of other opioid analgesics.
6. Ketamine is a short-acting phencyclidine compound that can be used for short, painful procedures, such as dressing changes in the burn ICU.

B. Sedatives.

1. Lorazepam is the preferred agent for the prolonged treatment of anxiety in the critically ill adult.
   a. Effects are similar to diazepam but is 5 to 10 times more potent.
   b. Onset of action is relatively slow, but it is longer acting.
   c. Administered with propylene glycol, which makes it precipitate in IV lines and can cause metabolic acidosis and acute tubular necrosis.
2. Midazolam is a short-acting benzodiazepine that has a short duration of action.
   a. Frequently combined with propofol and used for short-term treatment of anxiety in the critically ill adult.
   b. Also used for patients requiring prolonged ventilatory support in the ICU.
   c. Can cause hypotension and respiratory depression.
3. Diazepam is a weaker alternative that can be used in patients with prolonged hospital courses and recovery times.

4. Propofol is a lipid-soluble alkylphenol that is prepared as a lipid infusion and has excellent sedative and hypnotic effects.
   a. Does not provide analgesia.
   b. Mechanism of action not completely understood.
   c. Rapid levels of sedation can be quickly achieved and controlled.
   d. Discontinuation leads to rapid recovery, which makes it a popular choice for general anesthesia induction and maintenance.
5. Haloperidol is used to treat delirium in the ICU.
   a. Potential for causing arrhythmias, lowering seizure thresholds, and causing extrapyramidal reactions.

VIII. COMPLICATIONS

A. Under-treated pain and anxiety can lead to complications secondary to physiologic responses.
B. Constant stimulation of the autonomic nervous system and the release of humoral factors as a part of the stress response to injury, infection/sepsis, or surgery can lead to hemodynamic instability and increased demands on the heart, with ensuing myocardial ischemia or even infarction.
C. The stress response also causes insulin resistance, increased metabolic rate and protein catabolism, together with immunosuppression.
D. Adequate pain management can curb these once-considered physiologic responses and accelerate recovery after surgery or trauma.

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106 Management of the Obstetrical Patient in the Intensive Care Setting

Michael Sigman, Noah B. Rindos, and John G. Gianopoulos

I. OVERVIEW

A. General principles.

1. Maternal physiologic adaptation to pregnancy.

a. Cardiovascular.

i. Increased: cardiac output, blood volume.

ii. Decreased: peripheral vascular resistance.

b. Respiratory.

i. Increased: tidal volume and respiratory rate.

ii. Decreased: total lung capacity and functional residual capacity.

iii. No change: pulmonary artery pressure.

c. Hematologic.

i. Increased: blood volume, pH, coagulability.

ii. Decreased: hematocrit.

d. Renal.

i. Increased: renal artery perfusion, glomerular filtration rate (GFR), creatinine clearance, renal clearance of medications, and risk of urinary tract infection (UTI).

ii. Decreased: blood urea nitrogen (BUN), serum creatinine, and serum uric acid.

e. Gastrointesinal.

i. Increased: gastroesophageal reflux and risk of aspiration with intubation

ii. Decreased: motility and LES pressure.

2. Diagnostic radiation exposure.

a. Ultrasound and MRI are preferred to imaging that involves ionizing radiation.

b. There is a small risk of carcinogenesis in ionizing radiation at all gestational ages.

c. After the first 14 days, radiation exposure over 0.5 Gy may be associated with an increased risk of congenital malformations, growth restriction, and intellectual disability.

d. Abdominal/pelvic shielding should be used when possible.

e. Single-exposure films minimize radiation/risk to the fetus.

f. Computed tomography (CT) delivers radiation that is likely too low in dose to cause significant teratogenesis, however, should be avoided due to increased risk of carcinogenesis.

3. Medications and pregnancy.

a. Analgesics.

i. Short courses of opiates are tolerated.

ii. Codeine is teratogenic in the first 12 weeks.

b. Nonsteroidal antiinflammatory drugs (NSAIDs): are generally avoided due to possible premature closure of the ductus arteriosus. Short courses can be given in the second trimester to treat pain but are contraindicated in the third trimester.

c. Antibiotics.

i. No known fetal effect: penicillins, cephalosporins, erythromycin, clindamycin, and vancomycin.

ii. Streptomycin and kanamycin: fetal ototoxicity.

iii. Gentamicin can be used if necessary; monitor levels closely.

iv. Sulfonamides should be avoided in third trimester—associated with kernicterus.

v. Tetracycline is teratogenic.

vi. Fluoroquinolones are contraindicated throughout pregnancy due to effects on cartilage development.

d. Anticoagulants.

i. Coumadin: teratogenic in first trimester, later it carries risk of fetal bleeding.

ii. Heparin: does not cross placenta and is the anticoagulant of choice.

iii. Low molecular weight heparin: safe, change to unfractionated in third trimester—low molecular weight heparin associated with epidural hematoma with regional anesthesia.

e. Antihypertensives.

i. Avoid angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers—associated with fetal renal dysfunction and oligohydramnios.

ii. Sodium nitroprusside can lead to fetal thiocyanide poisoning.

iii. Hydralazine and labetalol are the first line IV medications in pregnancy.

iv. Any patient with elevated blood pressure should be evaluated for preeclampsia by sending a 24-hour urine collection, checking platelets ALT and AST (see section II below).

f. Pressors.

i. Because ephedrine, which has alpha- and beta-stimulating effects, tends to preserve uterine blood flow while reversing systemic hypotension, it may be the preferred pressor to try first. Phenylephrine has been used alone and in combination with ephedrine to reverse maternal hypotension with epidural anesthesia.

ii. Be aware that predominantly alpha-adrenergic agents improve maternal blood pressure but decrease uterine blood flow due to uterine artery vasoconstriction.

g. Tocolytics.
- **i.** Multiple classes: β-adrenergic, NSAID, calcium channel blockers, magnesium sulfate.
- **ii.** Limited efficacy, only used to gain 48 hours of additional pregnancy for the administration of betamethasone for fetal pulmonary development.
- **iii.** All have been associated with maternal pulmonary edema—use continuous pulse oximetry, avoid multiple agents as these increase the risk, treat with diuretics and supplemental oxygen, intubation or noninvasive ventilation.

II. HYPERTENSIVE DISORDERS OF PREGNANCY (PREECLAMPSIA)

A. General principles: 8% to 10% of pregnancies. Leading cause of obstetric morbidity/mortality.

B. Classification: chronic, gestational, preeclampsia/eclampsia, chronic with superimposed preeclampsia.

C. Etiology: unknown.

D. Pathophysiology: arteriolar vasospasm with intravascular volume depletion is the primary pathophysiologic alteration in preeclampsia.
1. Peripheral vascular resistance increases → hypertension (HTN) → proteinuria.
2. Decreased albumin in blood → decreased oncotic pressure.

E. Diagnosis.
1. Mild: sustained blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic developing after 20 weeks' gestation and proteinuria (>300 mg in a 24-hour collection).
2. Severe: one or more of the following: blood pressure >160 mm Hg systolic and/or 100 mm Hg diastolic (twice/6 hours apart); >5 g proteinuria; <500 mL urine output in 24 hours; cerebral or visual disturbances; pulmonary edema or cyanosis; epigastric or right upper quadrant pain. Impaired liver function; thrombocytopenia (<100,000/mm^3); fetal growth restriction.

F. Treatment: definitive treatment is delivery at 32 to 34 weeks for severe and 37 weeks for mild disease. If remote from term, expectant management is best for mild disease. Bed rest, intravenous (IV) fluids, treatment of HTN (labetalol or hydralizine), steroids for fetal lung maturity (before 34 weeks), and magnesium sulfate (seizure prophylaxis). Monitor labs: complete blood count (CBC), liver enzymes, 24-hour urine protein/creatinine clearance, coagulation studies, uric acid, and metabolic profile. Monitor fetal status (ultrasound and external fetal heart rate monitoring).

G. Complications: hemolysis, elevated liver enzymes, low platelets (HELLP), pulmonary edema, premature delivery, renal failure, abruption, and hypertensive encephalopathy. Eclamptic seizures are treated with IV magnesium (4-g loading dose and 2 g/hour).

III. OBSTETRIC HEMORRHAGE

A. General principles: significant cause of maternal morbidity, mortality, and fetal loss; 500 to 600 mL/minute flow to uterus at term; always localize the placenta by ultrasound before digitally examining the cervix.

B. Etiologies: placenta previa, placental abruption, uterine atony, retained placental, urogenital lacerations, and unrecognized coagulopathies.

C. Pathogenesis: previa—implantation of placenta over the cervix, abruption—separation of the placenta from the uterus before delivery of the fetus, atony—after delivery, the bleeding from the raw myometrial surface is halted by uterine contraction. Hemorrhage occurs when this fails to occur.

D. Diagnosis.

1. Third trimester bleeding: previa—painless vaginal bleeding, ultrasound shows placenta over cervical os. Abruption—painful vaginal bleeding, no previa on ultrasound, occurs in the setting of trauma, cocaine use.
2. Postpartum: loss >500 mL (vaginal delivery) or 1,000 mL (cesarean section), palpate for uterine tone, explore for retained placenta, examine for laceration, lab studies for clotting time.

E. Treatment.

1. Previa: bed rest, blood replacement, hospitalization near term and cesarean section.
2. Abruption: IV fluid and blood products, Kleihaur–Betke (a test for fetal hemoglobin in the maternal circulation) to assess for fetal maternal hemorrhage, delivery at term, expectant management and steroids if stable and remote from term.
3. Postpartum: uterine massage, uterotonics (pitocin, methergine [contraindicated with HTN], prostaglandins), uterine curettage, and repair of any lacerations.
4. Rhogam given to Rh negative, antibody negative women within 48 hours of delivery if they deliver an Rh-positive baby. Rhogam should be given to all women who have Rh-negative blood with any vaginal bleeding and also at 28 weeks.

F. Complications: fetal loss, placental accreta (growth into the myometrium), hysterectomy, and maternal hypotension with cerebral ischemia.

IV. AMNIOTIC FLUID EMBOLISM

A. General principles: sudden and acute cardiovascular and respiratory collapse at or around the time of delivery.

B. Etiology: entry of amniotic fluid into maternal circulation.

C. Pathogenesis: unknown.

D. Diagnosis: primarily clinical diagnosis of exclusion. Fetal squamous cells may be present in the maternal blood.

E. Treatment: early intubation and ventilation, inotropic and vasoconstrictive agents, invasive right-sided cardiac monitoring.

F. Complications: maternal death (>50%), disseminated intravascular coagulation (DIC).

V. HEMOLYTIC UREMIC SYNDROME/THROMBOTIC THROMBOCYTOPENIC PURPURA

A. General principles: rare in pregnancy, can be mistaken for preeclampsia.

B. Diagnosis.

1. Hemolytic uremic syndrome (HUS): renal failure, thrombocytopenia, and hemolysis.
2. Thrombotic thrombocytopenic purpura (TTP): renal failure, thrombocytopenia, hemolysis, fever, and neurologic changes usually associated with lack of function of the enzyme ADAMTS13.

C. Treatment: high-dose IV steroids, plasmapheresis.

D. Complications: bleeding and maternal mortality.

VI. BURN INJURIES

A. General principles: pregnancy does not alter the acute management of the burn victim. Fetal loss rate is correlated with severity of burn and development of complications.

B. Treatment: if remote from term—steroids for fetal lung maturity. If preterm labor and <30% burn, it is best to use tocolytics. Broad-spectrum antibiotics, tetanus toxoid, and immunoglobulin therapy are not contraindicated.

C. Complications: fetal loss—if maternal burn is >50%, then loss approaches 100%.

VII. TRAUMA

A. General principles: most common cause of maternal and fetal death in pregnancy. Maternal physiology may delay the manifestations of shock. Uterus is particularly susceptible to blunt and penetrating trauma in the third trimester. Fetal compromise may occur early after trauma. When evaluating hypotension, place the pregnant patient in left lateral decubitus position to optimize blood return from the lower extremities and minimize uterine compression of the IVC.

B. Treatment.

1. Blunt trauma: fetal assessment using ultrasound and continuous fetal monitoring (4-hour minimum, longer if abdominal pain, vaginal bleeding, or contractions). Kleihaur–Betke (fetal maternal hemorrhage). Rh immunoglobulin for Rh-negative mothers. Treat maternal injuries appropriately.
2. Penetrating trauma: uterus protects other maternal abdominal organs. Fetal injury is common in abdominal penetrating injury (66%) with high fetal mortality (40% to 70%). Management is controversial. Most advocate surgical exploration, but conservative management (imaging/observation) may be considered.

C. Complications: abruption, fetal compromise or demise, and fetal injury.

D. Any woman who is at 24 weeks or greater gestation should have a prompt evaluation by the obstetrical team. Women who are pregnant should receive the same level of care that a nonpregnant woman would receive—remember that the fetus poorly tolerates maternal death.

See Chapter 44 for other causes of acute respiratory failure in pregnancy and Chapter 89 for discussion of the HELLP syndrome.

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SECTION 12

SHOCK AND TRAUMA

Timothy A. Emhoff

107 Shock: An Overview

Kevin M. Dwyer and Timothy A. Emhoff

I. GENERAL PRINCIPLES

A. Definition.

1. Shock is a defined as inadequate end-organ perfusion that, left to itself, will result in anaerobic metabolism and ultimately end-organ failure and death.
2. *A momentary pause in the act of death. R Adams Cowley.*

B. Description.

1. Perfusion may be decreased systemically with obvious signs such as hypotension and tachycardia.
2. Perfusion may be decreased because of maldistribution as in septic shock, where systemic perfusion may appear elevated but ineffective.
3. Malperfusion may be isolated, leading to single-system failure such as in thrombotic or occlusive disease of the gastrointestinal (GI) tract or extremity.
4. Prognosis is determined by age, degree of shock, duration of shock, number of organs affected, previous organ dysfunction, precipitating factors, and genetic predisposition.

II. ETIOLOGY CLASSIFICATION OF SHOCK

A. Hypovolemic shock.

1. Initial loss of circulating intravascular volume results in decrease in cardiac preload, increase in afterload (vasoconstriction).

TABLE 107-1 Classification of Hypovolemic Shock

Hypovolemic shock (based on a 70-kg patient)	Class I	Class II	Class III	Class IV
Blood loss (mL)	Up to 750	750–1,500	1,500–2,000	>2,000
Blood volume (%)	Up to 15	15–30	30–40	>40
Pulse rate	<100	>100	>120	>140
BP	Normal	Normal	Decreased	Decreased
Capillary refill	Normal	Decreased	Decreased	Decreased
Respiratory rate	Normal	20–30	30–40	Distress
Urinary output (mL/h)	>30	20–30	5–15	<10
Mental status	Mild anxiety	Anxiety	Confused	Lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

2. Causes.
   a. Hemorrhage: trauma, GI bleeding, nontraumatic internal bleeding (such as aneurysm, ectopic rupture), liver adenoma, or vaginal bleeding (OB: abruption placenta).
   b. Nonhemorrhagic: fluid loss from the GI tract (vomiting, diarrhea, fistula), urinary losses (hyperglycemia with glycosuria, DI), prolonged evaporative loss (fever, hyperthermia), and internal fluid shifts (third spacing as with a bowel obstruction or pancreatitis).
3. Most common form of shock (fluid/blood loss).
4. All forms of shock have some component of decreased preload and benefit from intravascular infusion.
5. Clinical signs depend on the volume lost and patient response (Table 107-1). Usual symptoms include tachycardia, hypotension, decreased urine output, mental status changes, and tachypnea.
6. Initial treatment is with volume resuscitation with isotonic crystalloid solution, and, in addition, blood if from hemorrhage. In those patients requiring massive transfusion (>10 units packed red blood cells [PRBCs] in 24 hours), transfusing fresh frozen plasma (FFP) and blood in a 1:1 ratio while minimizing the use of crystalloids has been shown to have a clear survival benefit in trauma. Concomitant hemorrhage control is key to a successful resuscitation. Colloid infusion (albumin) has no value in the initial resuscitation of hypovolemic shock.

B. Obstructive shock.

1. Caused by a mechanical obstruction to normal cardiac output (CO) with a decrease in systemic perfusion.
2. Frequent causes: cardiac tamponade and tension pneumothorax.
   a. Clinical signs.
      i. Jugular venous distension.
      ii. Tachycardia.
      iii. Hypotension.

b. Ultrasound exam can quickly confirm pericardial fluid (tamponade) or pneumothorax (tension pneumothorax).

3. Other causes are massive venous thromboembolism and air embolism.

4. Treatment is maximizing preload (isotonic crystalloids) and relief of the obstruction.

C. Cardiogenic shock.

1. Caused by myocardial (pump) failure.

2. Most common cause is extensive myocardial infarction.

3. Other causes are reduced contractility (cardiomyopathy, sepsis induced), aortic stenosis, mitral stenosis, atrial myxoma, acute valvular failure, and cardiac dysrhythmias.

4. Treatment is maximizing preload, cardiac performance, and reducing afterload.

D. Distributive shock.

1. Caused by systemic vasodilatation from an inciting cause (infection, anaphylaxis, neurologic injury) resulting in systemic hypotension, and increased or decreased CO.

2. Sepsis is the most common precipitant of distributive shock. The endothelial toxicity and diffuse vasodilation are enhanced by messengers of the inflammatory response such as tissue necrosis factor–α (TNF-α) and interleukins 1 and 6.

3. Septic shock is associated with a brisk and often extensive inflammatory response. Despite a high CO, there is cellular hypoxia likely associated with disruption of mitochondrial function manifest as poor oxygen extraction/utilization.

4. In addition to sepsis, other causes of the systemic inflammatory response syndrome (SIRS) include posttraumatic shock and pancreatitis.

5. Treatment of septic shock is with massive volume to supplement preload, augmentation of blood pressure (BP) with vasoconstrictors as necessary, and treatment of the underlying cause.

6. Other causes of distributive shock are anaphylaxis, severe liver dysfunction, and neurogenic shock.

7. Neurogenic shock is due to cervical spinal cord injury with loss of sympathetic vascular tone. There is little inflammatory response. The patient has hypotension, bradycardia, and warm extremities. Treatment is with judicious volume expansion and a vasoconstrictor (low-dose dopamine or phenylephrine).

E. Endocrine shock.

1. Caused by hypothyroidism, hyperthyroidism with cardiac collapse, or adrenal insufficiency. Treatment is focused on the underlying disease.

2. Adrenal insufficiency may be a contributor to shock in critically ill patients. Patients unresponsive to treatment should be tested for adrenal insufficiency.

III. PATHOPHYSIOLOGY

A. The result of shock is tissue anaerobic metabolism, systemic acidosis with elevated lactate.

B. Cellular hypoxia leads to cellular ischemia. Ischemic cells are primed by alterations of calcium and adenosine 3′,5′-cyclic monophosphate (cAMP) and creation of superoxide radicals.

C. Endothelial cells under hypoxic conditions will have enhanced vascular permeability and less control over membrane transport functions.

D. Reperfusion can result in release of oxygen radicals that may cause further cell damage.

E. These processes activate neutrophils and the release of enzymes, oxidants, and proinflammatory cytokines.

F. The inflammatory response results in further cellular damage, third spacing, and activation of the coagulation system, leading to microcirculatory thrombosis, collapse, and further ischemia.

G. Microcirculatory collapse leads to multiple organ failure.

IV. DIAGNOSIS

A. Vital signs. Heart rate (HR), BP, temperature, urine output, and pulse oximetry are traditional measures to identify shock and judge the response to treatment, and most clinicians still rely on these. However, 50% to 85% of patients with normal or near-normal vital signs are still in shock as evidenced by ongoing systemic acidosis and declining end-organ function.

1. HR.

a. Tachycardia is an early sign of significant volume loss in shock.

b. The HR in young, elderly, or patients on β-blockers HR may not increase.

c. Bradycardia after prolonged hypotension may be a prelude to cardiovascular collapse.

2. BP.

a. Hypotension and narrowed pulse pressure are a sign of severe volume loss and shock.

b. Hypotension in the elderly may be significant for systolic BP < 110 mm Hg.

c. Mean arterial pressure (MAP) is a better guide to therapy than systolic BP.

3. Temperature.

a. Hyperthermia, normothermia, or hypothermia may be present in shock.

b. Hypothermia is a sign of severe hypovolemic and septic shock; more common in the elderly and immunocompromised patients.

B. Urine output.

1. A urine flow of <0.5 mL/kg/h is an early indication of organ dysfunction related to hypoperfusion.

2. This can be a delayed sign, as time (1 to 2 hours) may be needed to detect low output.

C. Pulse oximetry.

1. Continuously measured and early indicator of hypoxemia. May be invalid on the hypothermic, hypotensive, or vasoconstricted patient.

V. HEMODYNAMIC MONITORING

A. Indwelling arterial catheters give continuous BP measurements. Mean BP is more accurate/useful than systolic/diastolic BP, which can overestimate systolic and underestimate diastolic pressures.

B. A central venous catheter gives continuous and trended central venous pressure (CVP) measurements. CVO_2 saturation assays can be useful to guide initial crystalloid resuscitation when it is found to be low (<6 mm Hg; and <50% saturation).

C. Pulmonary arterial catheters, now rarely used, have been supplanted by noninvasive monitoring such as bedside cardiac ultrasound exam, Esophageal Doppler Monitoring (EDM) and Pulse Index Contour Analysis (PiCCO) all of which can relatively noninvasively help assess preload, cardiac function, and afterload on a rapid, repetitive basis.

1. Bedside ultrasound.
- **a.** Preload: assess IVC filling at the right atrial junction for respiratory variation: most accurate in the intubated patient: more than 13% variation during the respiratory cycle suggests fluid responsiveness in the hypotensive patient.
- **b.** Cardiac function.
  - **i.** LV size, uniformity of contractility, ejection fraction, valvular function.
  - **ii.** RV size/filling, valvular function.
- **c.** Afterload: while monitoring BP, reassess changes in cardiac function/chamber size with fluid resuscitation (as indicated).
- **d.** Limitations.
  - **i.** Extremely operator dependent: image acquisition and interpretation require training and practice.
  - **ii.** Expensive: initial costs of the bedside ultrasound machine: $30,000 to $40,000. Thereafter, each exam, which can be easily repeated, can be done with minimal or no cost (gel is the only disposable).

2. Esophageal Doppler Monitoring (EDM).
- **a.** Small Doppler probe placed in mid-esophagus to measure flow in the descending aorta.
- **b.** Through the use of algorithms (assumptions as to linear flow and aortic size), continuously measures the following:
  - **i.** LV stroke volume.
  - **ii.** Stroke volume variation (a measure of fluid responsiveness).
  - **iii.** Cardiac output (CO).
- **c.** In at least one study, has been shown to lessen morbidity in intraoperative resuscitation of femur fracture patients: helping to guide fluid needs and adequacy of CO.
- **d.** Limitations.
  - **i.** Variable accuracy in patients with nonsinus rhythms.
  - **ii.** Assumes laminar (non turbulent) flow parallel to the esophagus that is not always true.

3. Pulse Index Continuous Cardiac Output (PiCCO).

a. Thermistor-tipped arterial catheter, which continuously measures HR and arterial waveform. Analysis of this waveform then provides the following:
  i. Cardiac output (CO).
  ii. Stoke volume variation/pulse pressure variation: measures of fluid responsiveness.
  iii. Estimate of global end-diastolic volume as opposed to right ventricular end-diastolic pressure provided by a PA catheter.

b. Limitations:
  i. Requires arterial and central venous access.
  ii. Calibration greatly improved with the use of a PA catheter.
  iii. Assumes certain mechanical and elastic properties of the arterial tree, which may not be accurate in a particular patient.

VI. RESUSCITATION END POINTS

A. Lactic acid production.

1. Cells with inadequate oxygen will switch to anaerobic metabolism.
2. Lactic acid is a byproduct of anaerobic metabolism (type A lactic acidosis).
3. Elevation of serum lactate is a measure of the severity of shock. Elevated lactate is a global measure of hypoperfusion, and may not be elevated with regional hypoperfusion (loop of dead bowel). Lactate may be elevated in liver or kidney failure and may be of less value as an absolute number.
4. The rate of clearance of lactate is a better marker of adequate resuscitation rather than the absolute value: fall by 50% in first 6 hours of resuscitation generally indicates effective restoration of flow.

B. Base deficit.

1. Base deficit is the amount of base required to titrate whole blood to a normal pH.
2. The presence of an elevated base deficit correlates with the severity of shock and, in hemorrhagic shock, amount of blood loss: BD more negative than –6 usually require blood transfusion.
3. The correction of the base deficit is a guide to further resuscitation.

C. Muscle pH Monitoring.

1. Skeletal muscle represents the tissue bed most "down stream" of peripheral perfusion. Normal perfusion/pH equates to sufficient intravascular volume, while loss of circulating volume can be heralded by vasoconstriction and decreasing pH.
2. Near-infrared spectroscopy (NIRS) monitoring of the peripheral muscular bed (thenar eminence) has been touted to be able to monitor this process. Studies have shown that, however, it performs no better than monitoring the clearance of lactate and base deficit.

VII. TREATMENT

A. Rapid recognition and restoration of perfusion are the key to preventing multiple organ dysfunction and death with shock. In all forms of shock, rapid

restoration of preload with infusion of fluids is the first treatment. Crystalloid is first infused and then blood (in appropriate ratios to FFP) if shock is secondary to hemorrhage. Shock must be treated while identifying and controlling the cause. Further treatment of shock will depend upon its etiology.

VIII. HYPOVOLEMIC SHOCK

A. Rapid infusion of multiple liters of crystalloid is the treatment of hypovolemic shock due to loss of fluids or an increase in capacity (vasodilation). Large-bore venous access is needed, and central access may be necessary.

B. If the cause is hemorrhage, after 2 to 3 L of crystalloid, blood is transfused. If the patient will need "massive transfusion" (>10 units PRBCs/24 hours), such as from traumatic hemorrhage, then blood should be transfused in a 1:1 ratio with FFP. However, coagulopathy, hypothermia, and acidosis (lethal triad) will occur if the source of bleeding is not controlled.

C. Recent data from resuscitation of severe hemorrhagic shock from war wounds support the use of massive transfusion of blood and coagulation factors (FFP and platelets) in a 1:1:1 ratio.

D. Resuscitation is not complete until the base excess or serum lactate has decreased to an acceptable level. Patients with severe hypovolemic shock will have third space fluid with appropriate resuscitation.

E. Vasoconstrictors are rarely needed with pure hypovolemic shock.

F. A PAC or other more noninvasive hemodynamic monitoring (see above) may be helpful in guiding resuscitation in patients with severe shock, helping to target the particular cause/causes: preload, cardiac function, afterload.

IX. OBSTRUCTIVE SHOCK

A. The cause of the obstruction must be identified and relieved early.

1. Pericardiocentesis or pericardiotomy for a cardiac tamponade.
2. Needle decompression and tube thoracostomy for tension pneumothorax.
3. Ventilatory and cardiac support, possibly thrombolytics in addition to heparin for pulmonary embolism (see Chapter 90).

X. CARDIOGENIC SHOCK

(See Cardiac section of this manual.)

A. Optimize preload with infusion of fluids.

B. Optimize contractility with inotropes as needed, balancing cardiac oxygen demand. Consider dobutamine or milrinone.

C. Adjust afterload to maximize CO. This may involve using a vasoconstrictor if a patient is hypotensive with signs of vasodilation. Patients with cardiogenic shock may need vasodilatation to decrease their SVR and resistance to flow from a weak heart. Consider nitroprusside or nitroglycerin.

D. A B-type natriuretic peptide (BNP) level will be elevated in patients with congestive heart failure. Diureses may be indicated in patients.

E. A PAC or other noninvasive monitoring (see above) may be helpful to guide therapy in these patients.

F. The underlying cardiac cause needs to be treated if possible.

XI. DISTRIBUTIVE SHOCK

A. In septic shock, hypotension is due to toxin- or mediator-induced vasodilation (see Chapter 117).

B. Treatment is with aggressive fluid resuscitation (see Chapter 117). Once adequate volume status is established, pressors can be used to augment BP. Frequently, pressors are started during resuscitation. However, tissue perfusion will not be optimized unless optimal preload augmentation is achieved.

1. Dopamine was used in the past because of its splanchnic vasodilatation. However, this effect may be insignificant, and dopamine's initial effect is an increase in HR. Dopamine has no effect on mortality from septic shock.
2. Norepinephrine is a good vasoconstrictor and is the recommended pressor in septic shock once adequate volume is achieved.
3. Vasopressin has been used effectively in profound septic shock, especially when septic shock is refractory to norepinephine. There is evidence that natural vasopressin stores are low in patients in shock.
4. Doses of hydrocortisone sufficient to treat adrenal crisis should be given to patients with adrenal insufficiency.

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108 Hemorrhagic Shock and Resuscitation

Christopher P. Michetti and Timothy A. Emhoff

I. GENERAL PRINCIPLES

A. Definition.

1. Shock is a condition in which the amount of oxygen delivered to tissues is inadequate to maintain normal cellular function, that is, aerobic metabolism.

2. Hemorrhagic shock (HS) results from tissue hypoperfusion due to hypovolemia from blood loss.

B. Epidemiology.

1. Of those with severe, life-threatening injuries who survive to medical care, exsanguination is second to severe brain injury as the cause of death in the first hour.

C. Outcome.

1. Outcome is proportional to the duration and severity of shock.

2. Rapid identification of shock and initiation of treatment before hypotension occurs are essential to minimize morbidity.

3. Trauma patients with HS have improved outcomes when treated at a level I trauma center (highest level) as soon as possible after injury.

II. PATHOPHYSIOLOGY

A. Physiologic alterations.

1. Hypoperfusion after hemorrhage leads to tissue ischemia, a shift from aerobic to anaerobic metabolism, production of lactate release of inorganic phosphates, and metabolic acidosis.

a. Depletion of adenosine triphosphate (ATP), oxygen radical formation, and other processes of anaerobic metabolism result in cellular injury and eventually cell death.

2. The hypothalamic–pituitary–adrenal axis is activated by shock and results in release and elevation of several hormones.

a. Increased cortisol leads to hyperglycemia and insulin resistance, muscle breakdown, and lipolysis.

b. Release of vasopressin causes sodium and water retention.

c. Activation of the renin–angiotensin system produces angiotensin II, a vasoconstrictor.

3. Activation of the systemic inflammatory response results in release of proinflammatory mediators that can cause cell and organ dysfunction.
   a. Ischemia and reperfusion of tissues, especially gut, activate systemic inflammatory response.
   b. Cytokines such as tumor necrosis factor, interleukins 1 and 6 are released.
   c. Complement system is activated.
   d. Endothelial cells allow adhesion of activated neutrophils and their transmigration into tissues, where they cause tissue injury by releasing oxygen radicals and proteolytic enzymes. Loss of endothelial barrier function leads to transudation and intravascular fluid depletion.

B. Fluid shifts.

1. Triphasic response.
   a. Initial phase: response to bleeding is fluid shift from the interstitial space into capillaries to compensate for lost intravascular volume.
      i. Lasts from start of bleeding until bleeding controlled.
      ii. These fluid shifts occur in minutes after blood loss.
   b. Second phase: with resuscitation, fluid shifts from the intravascular space back to the interstitial space (the "third space").
      i. Lasts one to several days.
      ii. Interstitial space sequesters large amounts of fluids (the "capillary leak" phenomenon).
      iii. Patients become severely edematous and *simultaneously* intravascularly depleted.
      iv. Fluid intake markedly exceeds output.
      v. Fluid sequestration and resultant edema are obligatory and necessary in resuscitation from HS.
   c. Third phase: with restoration of endothelial integrity, fluid moves from the interstitial space to the intravascular space and is filtered through the kidneys, and diuresis occurs.
      i. Starts 3 to 5 days after injury.
      ii. Key sign of recovery from shock.

2. Common mistake among those inexperienced in shock resuscitation is to misinterpret the edema and highly positive fluid balance of shock patients as signs of increased hydrostatic pressure from congestive heart failure.
   a. Fluid intake/output balance is irrelevant in acute HS resuscitation.
   b. Tissue edema and increased body water are the natural result of successful HS resuscitation.
   c. Forced diuresis exacerbates tissue hypoperfusion by depleting intravascular volume.
   d. Overhydration, however, can lead to abdominal compartment syndrome, increased lung water, and poor tissue healing, further exacerbating trauma morbidity.

III. DIAGNOSIS

A. Classifications of HS.

1. Total circulating blood volume is 70 to 80 mL/kg in the adult.

2. Class I hemorrhage.
   a. Loss of up to 15% of total blood volume (0 to 750 mL in a 70-kg person).
   b. Characterized by normal vital signs and urine output, slight tachypnea, and slight anxiety.
3. Class II hemorrhage.
   a. Loss of 15% to 30% of total blood volume (750 to 1,500 mL).
   b. Characterized by normal blood pressure (BP), tachycardia, mild tachypnea, decreased urine output, and mild anxiety.
4. Class III hemorrhage.
   a. Loss of 30% to 40% of total blood volume (1,500 to 2,000 mL).
   b. Characterized by hypotension, tachycardia, tachypnea, decreased urine output, and anxiety and confusion.
5. Class IV hemorrhage.
   a. Loss of >40% of total blood volume (>2,000 mL).
   b. Characterized by severe hypotension and tachycardia, tachypnea, negligible urine output, and lethargy.
6. Note that BP is *normal* until significant blood loss occurs (Class III).
7. Tachycardia and decreased pulse pressure (systolic–diastolic) are the earliest reliable signs of shock.

B. Sources of hemorrhage.

1. There are only five locations of blood loss that can result in HS.
   a. Thorax.
      i. Hemothorax (blood in pleural cavity: 1,500 to 2,000 mL).
      ii. Diagnosis by chest radiograph, trauma-room ultrasound, or computed tomography (CT) scan.
      iii. Ninety percent of thoracic injuries can be treated with thoracostomy tube alone: evacuating the blood and reexpanding the lung (tamponading the bleeding source).
   b. Abdomen.
      i. Usually due to liver, spleen injury, or tears in the bowel mesentery.
      ii. Diagnosis by ultrasound (FAST exam), CT scan, or diagnostic peritoneal lavage.
      iii. Physical examination is *not adequate* to exclude bleeding in the abdomen.
      iv. Significant injuries (bowel rupture) and hemoperitoneum may be present with a normal abdominal examination.
   c. Pelvis and retroperitoneum.
      i. Exsanguination can result from pelvic fractures, especially posterior fractures.
      ii. Renal or major vascular injuries (pelvic veins/arteries) can result in significant retroperitoneal blood loss.
      iii. CT scan (with IV contrast) best exam for retroperitoneal hemorrhage from pelvic fracture, renal injury.
   d. Multiple long bone fractures.
      i. Can lose up to 1,500 mL of blood in each thigh from femur fractures.

ii. Can lose up to 750 mL of blood from humerus or tibia fracture.
iii. Diagnosis by radiography and physical exam.

e. External sites.
i. Bleeding from scalp lacerations, deep soft tissue wounds, major vascular injuries, and open fractures can all result in HS.
ii. Diagnosis by history (from scene) and physical examination of all wounds.
iii. Wounds should be carefully explored and never blindly probed (to avoid dislodging a hemostatic clot and rebleeding).
iv. Exsanguination from an external wound is best controlled with point pressure or tourniquet and then exploration in the operating room.

2. Intracranial bleeding or brain injuries do not cause shock unless so severe that brain death is imminent and hormonal imbalance has occurred.

IV. TREATMENT

A. Management of HS involves two goals: hemostasis and fluid resuscitation.

1. Both goals usually pursued simultaneously.

B. Hemostasis.

1. Identification and control of the source of bleeding are an absolute necessity in HS management.
2. The method of hemostasis depends on the cause and source of bleeding. Options include the following:
a. Surgery.
b. Endovascular techniques and embolization.
c. Application of direct pressure.
d. Correction of coagulopathy to allow hemostasis to occur on its own.
3. In some cases, "resuscitation to normalcy" is delayed until hemorrhage control is achieved.
a. Only applies to situations where surgery is planned as immediate definitive treatment:
i. Penetrating trauma, significant intraperitoneal bleeding, open wounds, ongoing intrathoracic bleeding.

C. Pitfalls in hemostasis.

1. Delay in surgery.
a. Hypotension from bleeding is an indication for immediate surgical consultation, because it indicates significant blood loss, and such patients have a high risk of requiring surgery.
b. Avoid attempts at interventional radiology or endovascular hemostasis in the setting of ongoing hypotension and active bleeding.
2. Not correcting hypothermia.
a. Hypothermia is a common and often-overlooked contributor to coagulopathy: prevention is key. Blood/blood products are stored cold and must be rewarmed on infusion.

b. Standard coagulation tests do not uncover hypothermia-induced coagulopathy, since blood is warmed in the laboratory before performing the tests.

3. Not correcting coagulopathy.

a. Frequent assessment of coagulation function should accompany any HS resuscitation. Again, prevention is key: use 1:1 FFP:PRBC ratios whenever massive transfusion is anticipated (>10 units of PRBCs within initial 24 hours).

D. Resuscitation.

1. The first priority for any bleeding patient is to ensure a patent, secure airway. The second priority is to ensure adequate breathing and ventilation. Hemostasis and fluid resuscitation are the third priority.

a. In clinical practice, all assessed and treated nearly simultaneously.

2. Resuscitation from HS includes stopping the bleeding and replacing the volume loss.

a. Direct localized pressure should be applied to any visible bleeding points. This also may preserve collateral flow.

i. Use of a tourniquet may be necessary if direct pressure on an extremity wound does not control the bleeding. Global ischemia is not a problem if the patient is rapidly (hours) brought to an operating room for repair/revascularization.

b. Resuscitation encompasses replacing volume loss and restoration of normal end-organ perfusion.

3. Fluid resuscitation.

a. Warm lactated Ringer solution or normal saline (crystalloid) is the preferred initial resuscitation fluid for HS, with initial rapid bolus of 2 L.

b. If hypotension persists after 2 L bolus of crystalloid, packed red blood cells and FFP in 1:1 ratio should be transfused.

i. Identification of the patient requiring massive transfusion.

(a) Hypotension, tachycardia, penetrating trauma with positive "FAST" exam; blunt trauma with positive "FAST" exam.

(b) Initial BD < −6.

(c) Initial Hct <30.

ii. Patient identified as meeting "criteria" for massive transfusion should receive FFP:PRBCs early on in a 1:1 ratio, minimizing further crystalloid use.

iii. General rule of HS resuscitation, not requiring massive transfusion, is to replace three times the volume of blood lost with crystalloid (e.g., 1 L of blood loss should be replaced with 3 L of crystalloid).

iv. Response to resuscitation.

c. Rapid response.

i. "Responders" become hemodynamically normal after the initial fluid bolus and remain so without continued boluses.

ii. Early surgical consultation is necessary due to the possible need for operative intervention.

d. Transient response.
  i. These patients respond to the initial fluid bolus, but again become hemodynamically unstable or show signs of decreased perfusion.
e. Continued fluid infusion and blood transfusion are required to maintain normal hemodynamics.
  i. These patients most often require rapid surgical intervention.
f. No response.
  i. Patients who show no response to fluid boluses and blood transfusion have continued and/or have exsanguinated their near-total blood volume and require immediate surgical intervention to stop bleeding.
  ii. Must keep in mind nonhemorrhagic causes of shock such as tension pneumothorax, cardiac tamponade, spinal cord injury, cardiogenic shock, adrenal insufficiency (associated with etomidate or recent steroid use), and septic shock (rare).

4. End points of resuscitation.
a. The goal of HS resuscitation is restoration of end-organ perfusion while stopping blood loss.
b. Traditional end points (normalization of BP, heart rate, urine output, capillary refill) are inadequate.
  i. BP does not equal cardiac output (CO) and therefore may not reflect normal perfusion.
  ii. Increased systemic vascular resistance (SVR) may raise BP, with little improvement in perfusion.
  iii. Patients with shock, but normal BP, are referred to as being in "compensated shock," since they are able to maintain BP despite bleeding and hypoperfusion.
c. Even experienced practitioners can be fooled by patients in compensated shock.
d. Failure to recognize compensated shock can result in underresuscitation and its sequelae.
e. Normalization of acidosis and oxygen consumption are the best current indicators of adequate resuscitation at cellular level.
  i. Normalization of base deficit and lactate are good indicators of the restoration of tissue perfusion.
  ii. "Lac time": halving the initial lactate level in the first 6 hours while normalizing BP, pulse, urine output, and end-organ perfusion is a good indicator of the restoration of aerobic metabolism.
  iii. Oxygen delivery and consumption can be calculated using a pulmonary artery catheter, but is rarely needed, except in the patient with significant cardiac dysfunction.

E. Pitfalls in resuscitation.

1. Not realizing early on the need for "massive transfusion" and the appropriate use of FFP:PRBC in a 1:1 ratio.
2. Overuse of crystalloids when FFP and PRBCs should be given. Massive use of crystalloid infusions is thought to promote immunocompromising inflammation, and survival benefit has been associated with 1:1 FFP to PRBC use for those requiring massive transfusion.

3. Albumin and other colloids.
   a. The majority of evidence shows higher mortality with use of albumin versus crystalloid in the initial resuscitation of HS.
   b. Massive transfusion: those patients who require >10 units PRBCs in first 24 hours realize a mortality benefit from the early use of FFP and PRBCs in a 1:1 ratio while limiting the use of crystalloid.
4. Vasopressors.
   a. Vasopressors increase SVR and raise BP, according to formula BP = CO × SVR. However, increased BP does not mean increased perfusion. Because normal tissue perfusion is the goal of shock resuscitation, vasopressors may have the opposite effect of decreasing perfusion through vasoconstriction and decreased CO.
   b. Must ensure adequate intravascular volume status before vasopressor therapy.
   c. There is some evidence that certain patients remain in "refractory shock" despite adequate resuscitation due to low circulating vasopressin levels, and improve with its infusion.
5. Diuretics.
   a. Well-resuscitated patients mobilize third-space fluids naturally 3 to 5 days after resuscitation.
   b. Induced diuresis (e.g., with furosemide) is unnecessary, and may be harmful when it reduces perfusion by lowering intravascular volume and CO.
   c. Because normal edema resulting from proper shock resuscitation is the result of an inflammation-related loss of endothelial barrier function (not cardiogenic failure), it is better accepted than treated with diuretics in the early stages of shock.
6. Bicarbonate.
   a. Bicarbonate combines with hydrogen ion to form water and carbon dioxide.
      i. CO_2 can diffuse into cells and worsens intracellular acidosis.
   b. It is not indicated for lactic acidosis from HS.
   c. Best treatment of acidosis from HS is restoring perfusion to ischemic tissues through volume resuscitation.

F. Investigational strategies.

1. Hypertonic saline.
   a. Seemingly should provide restoration of BP with lower volumes of fluid.
   b. Has anti-inflammatory properties.
   c. Studies in both shock (blood loss) and severe traumatic closed head injury (nonshock) have not shown a benefit from its initial use.
2. Delayed resuscitation.
   a. Entails limiting fluids and accepting low (adequate) BP until definitive control of hemorrhage achieved, to avoid popping the clot with normalized BP.
   b. Used only in patients with immediate OR access.

c. Contraindicated in brain injuries (hypotension worsens outcome); unproven in blunt trauma resuscitation *is* the treatment in those not requiring surgery or other invasive techniques to control the bleeding source.

3. Hemoglobin-based oxygen carriers.
   a. Solution of polymerized or cross-linked hemoglobin molecules able to carry and deliver oxygen.
   b. Clinical trials in humans thus far have not shown a survival benefit.

V. COMPLICATIONS

A. Multiple organ failure (MOF).

1. Patients who survive HS, but die in the hospital later, usually die of MOF or sepsis.
2. MOF results from a prolongation of the systemic inflammatory response.
3. Duration and severity of HS correlate with incidence of MOF.
4. Patients who get "massively transfused" with lower ratios (1:6, 1:8) of FFP:PRBCs and those who receive ongoing crystalloid with the massive transfusion have a higher mortality and incidence of MOF.

B. Coagulopathy.

1. Hypothermia.
   a. Most common cause of coagulopathy in HS.
   b. Significant coagulopathy begins at core body temperature <34°C.
   c. Causes a thrombocytopathy and is undetectable on usual laboratory tests of coagulation; thromboelastography will elucidate the problem.
      i. Prevention is key: warmed fluids/blood and external warming.
2. Platelet dysfunction and deficiency.
   a. Second most common cause of coagulopathy in HS.
   b. Hypothermia causes platelet dysfunction.
   c. Thrombocytopenia is common with massive HS when inappropriate ratios of FFP:PRBCs are given. A platelet "pack" (6 units) should be given after each 6 units of FFP/PRBCs.
   d. Degree of thrombocytopenia does not correlate directly with volume of blood loss.
   e. Platelet transfusion is indicated for platelet dysfunction (presence of microvascular bleeding or diffuse oozing) or platelet count <100,000/mm^3 with active bleeding.
3. Factor dysfunction and deficiency.
   a. Factor dysfunction in HS usually due to hypothermia (slows enzymatic reactions of coagulation). Beware patient anticoagulant use: coumadin, thrombin inhibitors (not directly reversible).
   b. Dilution of factors is possible with massive resuscitation, hence need for 1:1 FFP:PRBC use.
   c. Treat with normalizing body temperature, massive transfusion protocol with 1:1 FFP:PRBC use. Should NOT wait for "laboratory coagulation parameter abnormalities": too late.

4. Abdominal compartment syndrome.
   a. Primary (with intra-abdominal blood loss/pathology) or secondary (use of massive amounts of crystalloids without abdominal pathology, such as in severe burns.
   b. Increased intra-abdominal pressure: >10 mm Hg measured through a Foley catheter, usually >20 mm Hg causing the following physiologic changes:
      i. Increased peak airway pressures.
      ii. Decreased venous flow centrally (IVC collapse).
      iii. Decreased renal flow: decreased urine output.
      iv. Increased or persistent systemic acidosis.
      v. Difficult to treat/persistently elevated intracranial pressures.
   c. Treatment: open abdominal fascia with application of a closed/occlusive negative pressure system.

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109 Trauma: An Overview

Timothy A. Emhoff

I. THE PROBLEM

A. Annually 5 million deaths are due to trauma worldwide. In the United States, trauma is the leading cause of death between the ages of 1 and 44. In the year 2005 alone, 174,000 deaths were attributed to traumatic injury.

B. Although 80% of injuries can be cared for at local emergency rooms, the 20% of those seriously injured realize a 25% increase in survival if treated at a regional level I trauma center.

C. The leading cause of trauma deaths in the United States is motor vehicle crashes that accounts for 45,000 deaths annually. Motor vehicle crashes are predicted to become the third largest cause of death and disability worldwide by 2020.

D. Prevention of gun violence remains a public health challenge as gun-related deaths are the second leading cause of trauma deaths in the United States, far exceeding that in any other civilized country.

E. In the elderly, falls have become an increasingly prevalent mechanism of injury, carrying significant morbidity and even mortality from simple "standing height" falls.

II. LESSONS LEARNED IN TRAUMA CARE FROM MILITARY EXPERIENCE

A. Military medicine in the past two World Wars, Korea, Vietnam and, more recently, Iraq and Afghanistan has taught valuable principles of trauma care.

1. Early use of blood/blood products to treat hemorrhagic shock (WWII, Iraq, Afghanistan).
2. Early evacuation for definitive hemorrhage control and shock treatment (Vietnam, Iraq, Afghanistan).
3. Use of tourniquets, hemostatic agents for uncontrolled extremity hemorrhage: saving lives/limbs (Iraq, Afghanistan).
4. Increased ratios of plasma: packed red blood cells (PRBC) transfusions (damage control resuscitation) to treat hemorrhagic shock, yielding increased survival (Iraq, Afghanistan).
5. Immediate, nondefinitive surgery to stop hemorrhage, control sepsis, and revascularize extremities (damage control surgery) to prevent mortality from coagulopathy, acidosis, and hypothermia (Iraq, Afghanistan).

III. ADVANCED TRAUMA LIFE SUPPORT AND INITIAL APPROACH TO THE TRAUMA PATIENT

A. Advanced Trauma Life Support (ATLS), now in its ninth edition, is a course developed by the American College of Surgeons (ACS), taught around the world emphasizing one, safe way to provide the first hour of hospital care for the injured patient.

B. The A, B, C, D, Es of initial trauma care (*Primary Survey*) are (in order of priority).

1. **A**irway: assess for adequacy, need for definitive orotracheal intubation.
2. **B**reathing: ensure adequate ventilation and oxygenation. Quick assessment for pneumo/hemothorax with bedside ultrasound exam; need for urgent chest decompression/drainage.
3. **C**irculation: initial resuscitation with limited crystalloid (normal saline [NS] or lactated ringers [LR]) followed by early use of blood/blood products once hemorrhage is controlled.
4. **D**isability: neurologic examination, Glasgow Coma Scale (GCS) with attention to localizing signs of intracranial mass lesions, prompting early neurosurgical consultation.
5. **E**xposure/environment: completely expose the patient while maintaining normal core body temperature. Consider the mechanism of injury and prehospital circumstances of injury.

C. Adjuncts to the primary survey include:

1. Pulse oximetry: monitoring adequacy of oxygenation.
2. EKG monitoring: pulse rate/rhythm.
3. Urinary catheter: after ensuring safety of placement with perineal, rectal examination, to monitor renal function.
4. Orogastric tube: decompress the stomach, as needed.
5. Screening x-rays/ultrasound exam.
   - **a.** Chest x-ray (upright): lung and mediastinal structures.
   - **b.** Chest ultrasound: assess for "sliding" of pleural surfaces, indicating presence of pneumo/hemothorax.
   - **c.** AP pelvis x-ray: assess for fracture patterns associated with retroperitoneal (occult) bleeding.
6. An AMPLE history should be obtained: **A**llergies, **M**edications, **P**ast Illnesses/**P**regnancy, **L**ast meal, **E**vents/**E**nvironment related to the injury.

D. Only after the primary survey is completed, the patient is monitored, and resuscitation is underway should the *Secondary Survey* be done.

1. The ATLS *Secondary Survey* is a complete head-to-toe history and physical.
2. Head/CNS: scalp lesions, signs of basal skull fracture (Battle sign, CSF leak), signs of mid face, mandibular fracture. Pupils: comparative size and reactivity. GCS: eye opening, voice, motor responses.
3. Neck: immobilize (blunt trauma) until examined, and required x-rays are done. Signs of penetrating injury (beneath platysma) or blunt vascular injury: bruit, swelling, ecchymosis. A painful neck is a broken neck until proven otherwise: immobilize in a hard collar.

4. Chest: breath sounds (equal/symmetric); pain (rib fractures). Ultrasound exam for lack of pleural sliding (pneumothorax) and fluid (hemothorax).
5. Abdomen: pain, guarding, penetrations. FAST (*F*ocused *A*bdominal *U*ltrasound for *T*rauma) exam to asses for:
   a. Pericardial fluid (tamponade physiology).
   b. Intraabdominal fluid at interfaces: liver/kidney, spleen/kidney, pelvis: sign of intraabdominal hemorrhage.
6. Pelvis: stability, screening x-ray, fracture patterns associated with significant retroperitoneal bleeding (open book; posterior fractures); perineal exam, rectal exam: signs of urethral injury, prompting retrograde urethrogram.
7. Spine: pain or tenderness to palpation; motor/sensory exam (bilateral).
8. Extremities: open wounds; long-bone discontinuities, lax joints (dislocations), pulses, compartment tensions (sign of compartment syndrome): thighs, legs (see Chapter 116).

E. Adjuncts to the secondary survey include specialized diagnostic tests: x-rays, CT scan, MRI scan prompted by findings on primary and secondary surveys. These tests should be done when necessary for treatment purposes and when patient stability allows. This is the function of the trauma team: resuscitating and protecting the patient from further harm, triaging diagnostic tests, and involving consultants when patient care so warrants.

IV. MEASURING INJURY SEVERITY/PERFORMANCE IMPROVEMENT/ TRAUMA REGISTRIES

A. The Injury Severity Score (ISS) is an anatomic measure of injury severity. ISS ranges from 0 in patients with no injury, to 75 for injuries considered incompatible with survival. By definition, trauma patients with ISS > 15 are severely injured and have >10% mortality risk.

B. The GCS score is a clinical measure of severity of blunt brain injury based on eye opening (1 to 4), verbal response (1 to 5), and best motor response (1 to 6). The score range is 3 to 15. The GCS should be scored and recorded at the scene of the injury, at patient arrival in the emergency department (ED), and serially thereafter.

C. The Revised Trauma Score (RTS) is a physiologic measure of injury severity based on three factors: GCS, systolic blood pressure, and respiratory rate. RTS ranges from 0 to 12, with any score <12 used as an indication for trauma center level care in some locales. Many field triage schemes, however, now use anatomic, physiologic, and mechanism of injury criteria for transport to a trauma center, rather than on-scene scores (see reference: CDC: *Guidelines for Field Triage of Injured Patients: Recommendations of the National Expert Panel on Field Triage*).

D. ISS and RTS may be mathematically weighted and combined to estimate the probability of survival (P_s) for an individual trauma patient. These probabilities are frequently used for quality improvement efforts.

E. Quality improvement/performance improvement processes are an integral part of trauma center and trauma system programs. The ACS maintains the National Trauma Databank (NTDB), a resource of now over 3 million records. As part of that database, the Trauma Quality Improvement Project (TQIP) seeks to benchmark like trauma centers to each other comparing outcomes in various cohorts of patients. Using this feedback, it is expected that trauma centers will improve care and reduce morbidity/mortality.

F. Trauma registries are routinely in place now in all trauma centers, and the data are frequently aggregated at a state level. The NTDB contains >3 million individual trauma patient records.

V. TRAUMA CENTERS AND TRAUMA SYSTEMS

The concept of the "preventable trauma death" was instrumental in advent of trauma systems across the United States, typically organized at the state level. The system in San Diego, through an independent audit in 1982, was one of the first to show a survival benefit attributed to organized trauma care.

A. Statewide trauma systems must consider the following components: legislation; funding; injury prevention; notification (identification of incident); communication; prehospital emergency medical services, including scene care, triage, and transport; trauma center/acute care hospital services, including ED, operating room (OR), intensive care unit (ICU), and ward care; rehabilitation; disaster/mass casualties.

B. Triage guidelines are developed and adopted at a local or a state level. National guidelines were promulgated by the CDC in 2006 and examined for their basis in evidence in 2010 (see reference below: CDC). These are linked with destination protocols in an effort to get the right trauma patient to the right facility in the right amount of time using appropriate transportation modalities based on assessment in the field.

C. Trauma, perhaps more than any other disease, is time sensitive and requires a team approach. Each multidisciplinary trauma team needs a team leader, typically a surgeon in the United States trauma centers.

D. Many states designate trauma centers as levels I, II, and III, while others also include level IV hospitals that serve as system "entry points" and are not staffed/resourced to provide definitive trauma care.

E. Level I and level II trauma centers are able to provide full-spectrum care for the injured patient, including 24/7 neurosurgical and orthopedic specialty care. Although many states use the ACS trauma center verification standards, many others use state-specific criteria. The ACS standards can be found in "Resources for Optimal Care of the Injured Patient 2006."

F. Rehabilitation is critical to successful outcomes for patients who have suffered multiple injuries, although rehabilitation resources are all too frequently limited.

G. Statewide trauma systems are uniquely suited to act as the framework for mass casualty and disaster planning at the local, state, and national level.

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110 Transporting the Critically Ill Patient

Gina R. Dorlac, Jay A. Johannigman, and Nam Heui Kim

I. GENERAL PRINCIPLES

A. Transport of critically ill patients occurs any time a patient is moved from one physical location to another. This may be from the field, intra- or interfacility, by any means of transportation (stretcher, ground-based ambulance, rotary-wing aircraft, fixed-wing aircraft).

1. Essentials.

a. Pretransport evaluation (whether the transport takes minutes or hours!).

i. All patient movement has inherent risks and should only be done if the benefits of transport are significant and outweigh the risks.

ii. Risks of patient movement increase with severity of illness and duration of transport time.

iii. Best managed with a thorough checklist and a systematic approach.

iv. There are no absolute contraindications to transporting the critically ill patient.

v. There are many factors that may make patient movement high risk.

vi. The level of patient care provided should not be compromised during the period of transport.

b. Monitoring.

i. Patients who require monitoring before transport require monitoring during transport.

ii. Requires care provider who

(a) Can interpret the information.

(b) Responds appropriately to changes in status.

2. Care provided.

a. For longer transport distances and longer time periods:

i. Same monitoring and care must be provided as in the intensive care unit (ICU) (dosing of routine medications, deep vein thrombosis [DVT], prophylaxis, nutrition, decubitus ulcer prevention, etc.).

b. Short intrafacility transports.

i. Bare minimum requirements for intrafacility transports are the ability to provide advanced cardiac life support (ACLS) response and emergency airway management.

3. Caution: Many recommendations for care of the critical patient during transport are anecdotal rather than evidence based.

II. INDICATIONS

A. To obtain necessary procedures or diagnostic tests (radiographic studies, operating room, angiography suite) that cannot be performed at the bedside or for which better quality will result if done in designated area rather than at bedside.

B. To transfer a patient to a facility that provides a higher level of care, services unavailable in the current facility, or in a critically ill, but stabilized, patient to allow for family proximity.

C. To remove a patient from a high-risk area (combat zone, fire, chemical spill, or disaster area).

III. PROCEDURE

A. Patient evaluation.

1. Airway.
- **a.** Secure endotracheal tube, and ensure that the tube will not be obstructed by patient activity or motion (bite block).
- **b.** Consider delaying transport until 24 hours posttracheostomy.
- **c.** Consider prophylactic intubation for even minimal respiratory instability.

2. Ventilation.
- **a.** Familiarity with available transport ventilators is essential. Support from an experienced respiratory therapist is recommended. Transport ventilators exist that can match most, but not all, ICU ventilator modes.
- **b.** Allow room for deterioration in pulmonary physiology, especially for longer-duration transports. Patients on high FIO_2/high positive end-expiratory pressure (PEEP) have little margin for worsening.
- **c.** Consider transport on an ICU-type ventilator for patients with severe pulmonary impairment.
- **d.** Aggressively maintain pulmonary recruitment and PEEP.
- **e.** Always have a "rescue" mode of providing ventilation and oxygenation (such as a bag-valve mask and oxygen source).
- **f.** Consider elevation of head of bed if possible to minimize the risk for ventilator-associated pneumonia.

3. Cardiac.
- **a.** ACLS response must be immediately available.
- **b.** Consider preplacing defibrillator pads for those patients at highest risk of dysrhythmia (acute inferior wall myocardial infarction [MI] postthrombolytic therapy has 10% risk; new intraventricular conduction delay post-MI has 30% risk).
- **c.** Consider elective intubation for marginal patients: can decrease myocardial oxygen demand, and support the failing heart.

4. Metabolic.
- **a.** Electrolytes and acid–base status should be normal or normalizing.
- **b.** Patients on insulin infusion will require continued monitoring of blood glucose and may need a glucose source (such as a D5 drip); diabetic ketoacidosis will require in-transport glucose monitoring.

5. Infectious disease.
   a. Appropriate isolation for patients with communicable disease.
   b. For known infection, consider possibility of sepsis progressing. Anticipate potential for need to broaden antibiotic coverage and have vasopressor agents available during transport.
6. Orthopedic.
   a. Fractures must be stabilized pretransport; consider external fixation; consider whether traction can be maintained during transport.
   b. Evaluate for extremity compartment syndrome before transport; anticipate the possibility of development of extremity compartment syndrome during long transports.
7. Neurologic.
   a. Many patients will require deeper levels of sedation to facilitate safe transport; avoid inadvertent removal of therapeutic devices. Consider neuromuscular blockade when appropriate. During short transports, sedation may be managed by intermittent bolus therapy; for longer transports, continuous infusions should be considered.
   b. Consider intracranial pressure (ICP) monitoring in critical brain-injured patients in whom a consistent neurologic examination is not available. ICP monitoring must be continuous. Elevation of the head of bed during transport is important.
   c. Anticipate worsening intracranial hypertension and be prepared to treat (hypertonic saline, mannitol, or acute mild hyperventilation).
   d. Seizure prophylaxis should be given pretransport, and acute treatment should be available.
   e. Anticipate potential for diabetes insipidus, and consider having desmopressin (DDAVP) available.
8. Burns.
   a. Thermoregulation can be difficult in the transport environment. Aggressively maintain normothermia using any means available: ambient temperature control, blankets, and head covering.
   b. Avoid burn wound manipulation in transport: wounds should remain dressed.
   c. Anticipate the development of compartment syndromes, and consider the need for escharotomies.

B. Equipment considerations.

1. Ventilator, infusion pump, monitor, suction, and defibrillator must all be approved for use in the transport vehicle; have adequate battery power for transport and/or ability to be plugged into transport vehicle and be checked for operability before the transport.
2. If in-transport laboratory testing is required, point-of-care testing device and supplies must be available and calibrated before transport.
3. Supplies to include medications, intravenous fluids, batteries, and oxygen must be sufficient for entire transport time, including unexpected delays. Carry extra batteries and oxygen canisters.

C. Team composition.

1. Varies depending on patient numbers and acuity of patients. Highest demand in flight is typically on nursing duties. Requirement for a physician in attendance will depend on patient acuity and availability of the physician to join team in case of deterioration. A trained critical care transport team may prevent adverse technical incidents during transport.

D. Transport physiology.

1. Patients transported at altitude have additional physiologic stresses that must be considered.
   - **a.** Anticipate gas expansion in a hypobaric environment (consider chest tubes in patients with pneumothorax or potential to develop one).
   - **b.** Decreased ambient partial pressure of oxygen (decreased ability to oxygenate).
   - **c.** Lower humidity.
   - **d.** Less well-regulated temperature.

IV. POSTPROCEDURE CONSIDERATIONS

A. The care of the patient is the responsibility of the transporting team until appropriate assessment and hand-off are made at the receiving facility.

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111 Head Trauma

Joshua J. Wind, Joshua M. Ammerman, James M. Ecklund, and Nam Heui Kim

I. GENERAL PRINCIPLES

A. Traumatic brain injury (TBI) is a leading cause of death and long-term disability and results in an enormous economic cost to society. More than 1.7 million head injuries occur each year, accounting for 275,000 hospitalizations and 53,000 deaths. At least 5.3 million or 2% of the U.S. population live with disabilities resulting from TBI. Outcomes from TBI have improved with improved critical care and multidisciplinary management teams made up of trauma surgeons, intensivists, neurosurgeons, and others. The use of advanced monitoring techniques and evidence-based approaches to TBI management have also contributed to these improved outcomes.

II. ETIOLOGY

A. Head trauma can be categorized as closed or penetrating. The most frequent causes for closed TBI are motor vehicle accidents, falls, and assaults. Frequent causes of penetrating TBI are gunshot wounds or fragmentation injuries in the military population.

III. PATHOPHYSIOLOGY

A. *Primary brain injury*—occurs at time of injury as a result of direct trauma to brain tissue.

B. *Secondary brain injury*—occurs after initial injury, causing additional insults to the brain. This is usually secondary to hypoxia, hypotension, intracranial hypertension, and/or complex inflammatory cascade.

C. Increased intracranial pressure (ICP) may be a result of mass effect imparted during the primary injury, such as a hematoma, or as a result of edema from secondary processes. Much of the management of TBI is aimed at preventing or treating elevated ICPs.

1. Monro-Kellie doctrine → The skull is a rigid compartment containing brain tissue, cerebrospinal fluid (CSF), and intravascular blood. Because this space is unable to expand, any change in its contents (intracranial mass lesion or diffuse edema) must be followed by a subsequent reduction in other components in order to compensate. This eventually leads to a decrease in cerebral blood flow and brain perfusion.

2. Herniation occurs when ICP rises to the point where brain contents herniate through a skull compartment opening (either through the tentorial incisura, below the falx cerebri, or through the foramen magnum), occluding blood flow to the brain.
3. Brain death occurs when cerebral edema and herniation eliminate adequate blood flow to the brain, resulting in widespread infarction. Brain death is defined as the irreversible cessation of all brain cortical and brainstem functions.

IV. DIAGNOSIS

A. History of traumatic event and neurologic status at the scene.
B. Neurologic examination.
   1. Examination for scalp lesions, skull fractures (open or closed), and CSF leak.
   2. Pupil size and reactivity.
   3. Motor and sensory examination.
      a. Uncal herniation syndrome includes ipsilateral fixed, nonreactive pupil, and contralateral hemiparesis (rarely ipsilateral–"Kernohan notch phenomenon").
      b. Peripheral and central reflex examination.
      c. Glasgow coma scale (GCS) (Table 111-1).
C. Radiographic studies.
   1. Noncontrast computed tomography (CT) scan of the head is often used as a primary radiographic study for evaluation of a patient with a head injury. It is an adequate modality for evaluating most skull fractures, mass lesions including hematomas and contusions, and other processes including hydrocephalus or cerebral edema. May also be used serially for patients whose neurologic exams are not obtainable or unreliable.
   2. CT angiography is the screening test of choice to rule out blunt vascular injury (BVI) in the trauma patient. Injury patterns which are associated with BVI are c-spine fractures, midface fractures, and lateralizing

TABLE 111-1 Glasgow Coma Score

Eye	Motor	Verbal
1. No opening	1. No motor response	1. No verbal response
2. Open to pain	2. Decerebrate posturing	2. Incomprehensible sounds
3. Open to voice	3. Decorticate posturing	3. Inappropriate words
4. Open spontaneously	4. Withdraws to pain	4. Confused response
	5. Localizes to pain	5. Oriented response
	6. Follows commands	

The components are added together for a cumulative Glasgow coma score. If the patient is intubated, a score of 1 T is used for the verbal component.

neurologic signs not explained on brain CT. CT angiography, magnetic resonance (MR) angiography, or conventional cerebral angiography may also be used to characterize any lesion found.

V. TREATMENT

A. Ensure adequate airway, breathing, and circulation (systolic blood pressure [SBP] > 90, SpO_2 > 90). Both hypotension and hypoxia are associated with significantly increased mortality and morbidity in patients with severe brain injury (GCS ≤ 8).

B. Urgent neurosurgical consultation is required for significant mass lesions, such as epidural hematomas (EDH), subdural hematomas (SDH), depressed skull fractures, contusions, intraparenchymal hematomas, and for penetrating brain injuries. Guidelines for surgical management of these lesions are included in the Suggested Readings.

C. ICP monitoring is indicated in all patients with GCS 3 to 8 who have a CT revealing lesions or edema or patients with normal CT when two or more of the following are present: age older than 40, motor posturing, and SBP < 90 mm Hg. Ventriculostomy is desirable when feasible, as it is more cost-effective, accurate, and allows CSF drainage to aid in the treatment of elevated ICP. Other types of ICP monitors (intraparenchymal fiberoptic monitors, for example) are acceptable but have the added complexity of signal drift and the inability to recalibrate once placed.

D. Once ICP monitoring has been initiated, the goal is to maintain ICP < 20 mm Hg and to preserve cerebral perfusion pressure (CPP) ideally above 60 (CPP = mean arterial pressure – ICP). CPP < 50 should be avoided; however, aggressive attempts to maintain elevated CPP (i.e., >70) may result in pulmonary complications such as acute respiratory distress syndrome (ARDS).

E. A three-tiered management algorithm for TBI and elevated ICP is presented below:

1. First-tier measures.
   - **a.** Elevate head of bed to 30 to 45 degrees.
   - **b.** Keep neck straight to avoid jugular outflow obstruction.
   - **c.** Avoid hypotension and hypoxia.
   - **d.** Ventilate to normocarbia ($PaCO_2$ 35 to 40).
   - **e.** Light sedation.
2. Second-tier measures.
   - **a.** Heavy sedation.
   - **b.** Paralysis (if sedation fails).
   - **c.** CSF drainage with ventriculostomy.
   - **d.** Mannitol or hypertonic saline.
   - **e.** Temporary mild hyperventilation ($Paco_2$ 30 to 35): while other measures are instituted to protect CPP.
3. Third-tier measures.
   - **a.** Decompressive craniectomy.
   - **b.** Barbiturate coma.
   - **c.** Hypothermia: clearly beneficial to help control raised ICP but not clear that this modality yields better outcomes/lower mortality.

4. Early hyperventilation and mannitol before ICP monitoring should be limited to patients with evidence of herniation as a temporizing measure only.

F. Multiple other monitoring tools can provide additional input to guide therapy, including brain tissue oxygenation ($PbtO_2$), jugular venous O_2 saturation ($SjvO_2$), cerebral blood flow, and continuous electroencephalogram (EEG).

VI. COMPLICATIONS

A. The primary complication of TBI is secondary brain injury that can compound the neurologic morbidity and mortality. The most severe result is progression to herniation and brain death.

B. Systemic complications of TBI.

1. Diabetes insipidus—hypothalamic nuclei produce arginine vasopressin, which functions at the collecting duct of the kidney to reabsorb free water. Injury to these nuclei, most commonly seen in very severe head injuries, results in the inability to concentrate urine (very low urine Na) and subsequent elevation of serum osmolality. Excessive urine losses can easily dehydrate the patient in a few short hours.
2. Syndrome of inappropriate antidiuretic hormone (SIADH)—excessive release of arginine vasopressin, resulting in excessive concentration of urine and dilution of serum electrolytes, such as sodium.
3. Cerebral salt wasting—poorly understood condition where volume *and* sodium are excreted in the urine, resulting in hypovolemia and hyponatremia. Withholding fluids in these patients (as in hyponatremia from fluid overload) can lead to hypotension, ATN, low CPP, and brain ischemia.
4. Seizures—can occur early (first 7 days) or late. Prophylactic anticonvulsants recommended for the first 7 days for severe brain trauma and for penetrating brain injury. Phenytoin is best studied, small studies and a meta-analysis show that levetiracetam may have similar results and is also being used for the early seizure prophylaxis. Valproate has also used for this purpose but may be associated with higher mortality rate.
5. Coagulopathy—release of tissue factors may result in increased fibrinolysis and hypocoagulable state. This may progress to disseminated intravascular coagulation (DIC).
6. Cardiopulmonary complications—myocardial infarction, cardiomyopathy, ARDS, and heart failure.
7. Deep venous thrombosis and pulmonary embolus—pneumatic compression devices are recommended initially; prophylactic doses of anticoagulation can be considered after 48 hours if brain lesions show no progression and considered safe. Inferior vena cava filter (IVCF) may be considered for patients considered high risk for chemical DVT prophylaxis and at high risk for development of thromboembolic events.
8. Infection—patients with head injuries are at risk for ventilator-related pneumonia, line sepsis, and other infections. CSF leaks increase risk for meningitis. Antibiotic use during ventriculostomy placement is indicated, but there is no clear indication for continuous antibiotics while ventriculostomy is in place.
9. Nutrition—patients should attain 100% to 140% of protein/calorie demands by 1 week after injury.

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112 Spinal Cord Trauma

Howard B. Levene, Michael Y. Wang, Barth A. Green, and Timothy A. Emhoff

I. EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE

A. Affects approximately 11,000 Americans per year.
B. A total of 200,000 patients living with spinal cord injury (SCI).
C. Typically affects young males (15 to 29 years), but a growing trend of middle-aged and elderly patients due to lifestyle habits and improved survivability of injuries.
D. Etiology.

1. Motor vehicle accident 47%.
2. Falls 23%.
3. Violence 14%.
4. Sports/recreation 9%.
5. Other 7%.

II. NEUROLOGIC INJURY

A. SCI can be classified by the following:

1. Mechanism (penetrating vs. blunt trauma).
2. Level (cervical, thoracic, or lumbar).
   a. Designated as the lowest spinal segment with completely normal function.
3. Neurologic injury (degree of impairment), frequently designated by the American Spinal Injury Association (ASIA) grade (Table 112-1).
   a. Grade A Complete: no sensory or motor function preserved in sacral segments S4-5.
   b. Grade B Incomplete: sensory, but not motor, function preserved below neurologic level and extends through sacral segments S4-5.
   c. Grade C Incomplete: motor function preserved below neurologic level with muscle grade less than antigravity strength.
   d. Grade D Incomplete: motor function preserved below neurologic level with muscle grade greater than or equal antigravity strength.
   e. Grade E Normal: sensory and motor functions normal.

B. Complete SCI.

1. No preservation of motor function and/or sensation three spinal segments below the level of injury.
2. Complete injuries above T6 can be associated with neurogenic shock (usually with cervical spine injury).
   a. Hypotension from interruption of sympathetics.
   b. Bradycardia from unopposed vagal (parasympathetic) output.

TABLE 112-1 American Spinal Injury Association Grading Scale for Spinal Cord Injury

Clinical grade	Neurologic examination
A	No motor or sensory function preserved
B	Sensory but no motor function preserved
C	Nonuseful motor function preserved (less than antigravity strength)
D	Motor function preserved but weak
E	Normal motor and sensory function

c. Hypothermia: vasodilation.
d. Transient loss of all neurologic function resulting in flaccid paralysis and areflexia: spinal shock.

C. Incomplete SCI.

1. Any preservation of motor and/or sensory function three spinal segments below level of injury, including sphincter tone or sacral sensation: so-called "presacral sparing."
2. Denotes improved likelihood of recovery of function.

D. Specific incomplete SCI syndromes.

1. Central cord syndrome.
a. Occurs in two patient populations: young athletes with congenital cervical stenosis and, more commonly, in the elderly with acquired cervical stenosis from spondylosis.
b. Hyperextension injury.
c. Upper extremity weakness out of proportion to lower extremity weakness: lower extremities recover more than upper: usually associated with residual upper extremity weakness.
d. No evidence of cervical spine fracture.

2. Brown-Sequard syndrome (usually from penetrating mechanisms).
a. Spinal cord hemisection.
b. Loss of *contralateral* pain and temperature sensation; *ipsilateral* loss of proprioception, vibratory sensation, and motor function.

3. Anterior cord syndrome.
a. Spinal cord infarction in distribution of anterior spinal artery (anterior two-thirds of cord).
b. Complete loss of motor function and loss of pain and temperature sensation, but preserved posterior column function (proprioception and vibratory sensation).

4. Conus medullaris syndrome.
a. Associated with thoracolumbar junction fracture.
b. Early loss of sexual and sphincter function.
c. Symmetric "saddle" loss of motor and/or sensory function in lower extremities.

III. PATHOPHYSIOLOGY

A. SCI is comprised of primary and secondary injury mechanisms.

1. Primary injury mechanisms.
- **a.** Kinetic energy transferred to neural elements during trauma.
- **b.** Compression from bone, cartilage, hematoma, or foreign bodies.
- **c.** Results from:
  - **i.** Movement and stressing of the spine beyond its physiologic limits in hyperflexion or hyperextension.
  - **ii.** Retropulsion of bone or disc into the spinal canal.
  - **iii.** Dislocation of the spinal column.
  - **iv.** Direct laceration or transection of the cord (penetrating injury).

2. Secondary injury mechanisms.
- **a.** Systemic hypoxia and hypotension from neurogenic shock, hypoperfusion, hypoxia, or other systemic injuries resulting in hemodynamic, pulmonary, or respiratory instabilities.
- **b.** Local vascular insufficiency of the cord from trauma.
- **c.** Ongoing spinal compression (herniated disk, compressive hematoma, malalignment).
- **d.** Biochemical changes: free radicals, cytokines (see reference below).
- **e.** Electrolyte shifts (in to/out of the damaged cord).
- **f.** Edema.
- **g.** Loss of energy metabolism with decreased adenosine triphosphate (ATP) production.

IV. INITIAL ASSESSMENT AND STABILIZATION

A. Primary trauma survey (**A**irway, **B**reathing, **C**irculation, **D**isability, **E**xposure [ABCDE]).

1. Special attention to hemodynamic stability to maintain cord perfusion and management of neurogenic shock.
- **a.** Judicious crystalloid fluid resuscitation.
- **b.** Search for and control of sources of ongoing hemorrhage.
- **c.** Early use of pressors (alpha-adrenergic) to maintain mean arterial pressure (MAP) > 80 mm Hg to combat loss of sympathetic tone.

2. Maintenance/reestablish spinal alignment and immobilization: "screening" lateral c-spine x-rays are no longer done: the neck is kept immobilized and neutral until a helical computed tomography (CT) scan is evaluated for injury.

B. Neurologic examination (completeness and level of injury).

C. Radiographic assessment: liberal use of helical CT: significantly better than "screening" plain x-rays at all levels.

1. Mechanism and degree of spinal column injury.

2. Degree of persistent neural compression.

3. Detection of second-site, noncontiguous spinal injuries (occur in 15%) of SCI patients.

D. Early intervention to prevent the onset of delayed sequelae (respiratory, cutaneous, gastrointestinal, thromboembolism).

V. ASSESSMENT OF SPINAL COLUMN STABILITY

A. Definition.

1. Clinical instability: potential for further neurologic injury if allowed to bear normal physiologic loads.

2. Radiographic instability.

a. Abnormal motion on dynamic x-rays (e.g., >3.5-mm subluxation or >11 degrees of angulation in the cervical spine).

b. Fracture or alignment pattern consistent with severe instability (e.g., spondyloptosis with a fracture dislocation or Chance fracture) (Fig. 112-1).

c. Substantial destruction of the bony/ligamentous elements on imaging (e.g., two of three columns being injured) (Fig. 112-2).

3. Predictors of delayed instability.

a. Fracture patterns that would be predicted, if left untreated, to result in late neural compression, deformity, or pseudarthrosis.

B. Instability of the spinal column militates for maintenance of spinal precautions and bracing. In many instances, surgical realignment, fixation, and fusion will be necessary.

C. Missile injuries rarely destabilize the spine.

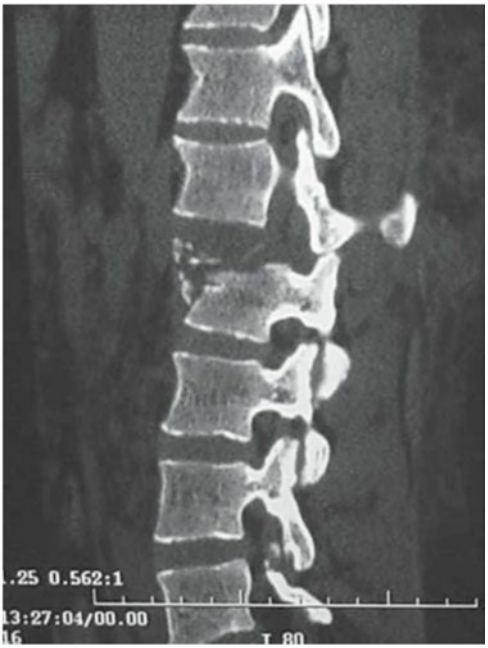

Figure 112-1. Chance fracture.

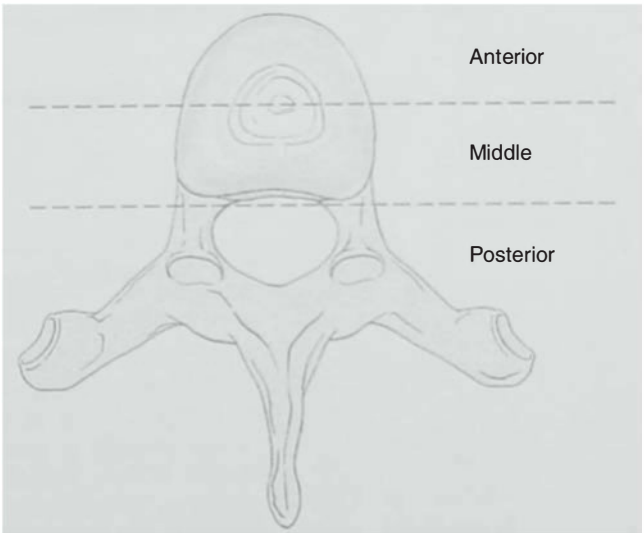

Figure 112-2. Three-column injury model.

VI. TREATMENT

A. Management in the field.

1. Airway management, maintenance of adequate blood pressure (BP) (i.e., systolic blood pressure [SBP] > 120, MAP > 80).
2. Major blunt trauma victims whether conscious or unconscious should be deemed to have SCI until proved otherwise. Field "neck clearance" should not be done.
3. Cervical collar in combination with rigid backboard should be used to immobilize spine.

B. Acute hospital management.

1. Assessing for spine injury/"clearing the neck" consists of the following:
   a. Clinical exam: If no pain on active motion and no motor or sensory deficits without a concerning mechanism of injury (fall from height, high-speed motor vehicle crash [MVC]) in an awake, cooperative patient with no distracting injury, the neck may be "cleared" without radiographic studies.
   b. *With concerning mechanism of injury*: "Clearing the neck" should consist of a normal exam (with clear mental status, no distracting injury or inebriation) and normal helical CT scan with coronal, sagittal, and axial reconstructions.
   c. In the obtunded or unexaminable patient, many trauma centers are now "clearing the neck" with a normal helical CT; others require additionally a normal magnetic resonance imaging (MRI) scan within 72 hours of injury for "clearance."

d. Any palpable area of pain is a fracture/injury until proven otherwise.
e. CT scan is a better screening tool than plain x-ray at all levels.

2. Degree of stability.
a. Rigid immobilization with cervical traction and kinetic treatment table or halo-vest orthosis for unstable/misaligned fractures.
b. Nonrigid immobilization with cervical collar or thoracolumbosacral orthosis for stable fractures.

3. Need for neurologic decompression.
a. Closed reduction and traction for dislocation or subluxation with cord and/or root compression to restore normal alignment.
i. Neurologic deterioration after reduction from herniated disk.
ii. Recommend MRI before reduction in obtunded or incomplete patients.
b. Open surgical reduction and decompression for irreducible dislocation, bone/disk fragments in the canal, or epidural hematoma causing persistent cord and/or root compression.

3. Timing of decompressive surgery.
a. Early decompression may mitigate secondary injury mechanisms but will not affect irreversible primary injury mechanisms.
b. Early evidence from the STASCIS trial (see reference below) indicated that decompressive surgery within 24 hours of injury, in selected patients, resulted in significantly better functional recovery (two ASIA grade levels).

C. High-dose steroids.

1. No longer considered standard of care.
2. Special circumstances: nerve root compression and postreduction edema may warrant their use, but on a case-by-case basis.

VII. SEQUELAE AND COMPLICATIONS

A. Cardiovascular.

1. Hypotension and bradycardia from neurogenic shock (sympathectomy effect).
a. Thirty percent of "high" (C1-5) injuries will have neurogenic shock on admission.
b. Management with titrated dopamine or phenylephrine (low dose) to support BP.
c. Atropine to increase heart rate: rarely needed; only if bradycardia associated with ventricular escape or hypotension.

2. Autonomic hyperreflexia (periodic autonomic instability triggered by stimuli such as bladder filling or catheterization).
a. After spinal shock has cleared and reflexes have returned (days after injury).
b. Occurs in patients with SCI above T6.
c. Exaggerated autonomic responses, including headache, flushing, diaphoresis, and paroxysmal hypertension.

d. Can be life threatening if associated with hypertension (central nervous system [CNS] hemorrhage).
e. Treat by elimination of offending stimuli: usually bladder distension, unrecognized injury (fracture), tissue injury (decubitus).

B. Pulmonary.

1. High cervical injuries above segments C3-5 that contribute to phrenic nerve may leave patients ventilator dependent or with weak cough mechanism to clear airway secretions or obstructions: almost all will require tracheostomy.
2. All injuries above T5 will have significant loss of inspiratory/expiratory force and volume given intercostal denervation: few will require tracheostomy.
3. Aggressive pulmonary toilet is required to prevent atelectasis and pneumonia.
4. Placement of an abdominal binder can minimize paradoxical respiratory effort and increase respiration.
5. Immobilization makes patient vulnerable to deep vein thrombosis (DVT) and pulmonary embolism (PE).
6. DVT prophylaxis should be undertaken with subcutaneous (SQ) heparin or low molecular weight heparin (LMWH) combined with sequential compression devices for lower extremities.
7. Retrievable inferior vena cava (IVC) filter or regular duplex ultrasound surveillance should be considered.

C. Gastrointestinal.

1. Most patients with acute SCI present with partial ileus.
2. Nasogastric or orogastric tube should be placed to prevent gastric distension and perforation.
3. H_2-receptor antagonist or proton pump inhibitor should be used to prevent stress ulcers.
4. Not all cardinal signs of acute abdomen are present in spinal cord–injured patients: imaging is necessary.

D. Genitourinary.

1. Most spinal cord–injured patients cannot void spontaneously.
2. Indwelling Foley catheter used until patient hemodynamically and neurologically stable.
3. Intermittent straight catheterization used after Foley removed to decrease incidence of urinary tract infections (UTIs).

E. Infectious disease/fever workup.

1. White blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) as markers of infection; chest x-ray (CXR) for atelectasis or pneumonia.
2. Urine analysis and urine cultures for UTI.
3. Duplex ultrasound of lower extremities for DVT.
4. Liver function tests (LFTs), total and direct bilirubin, and amylase and lipase, for hepatitis, acalculous cholecystitis, or pancreatitis.
5. Blood cultures can be helpful when bacteremia or endocarditis is suspected.

6. Inspection of skin/wound for infection, pressure ulceration.
7. Bone scan and plain x-rays for heterotopic bone formation (late complication).

F. Cutaneous.

1. Decubitus ulcers from prolonged positioning on pressure points.
2. Prevention with frequent turning protocol, daily bathing and lotion application, and careful skin inspection.
3. Early use of rotating beds and alternating inflated air mattresses.
4. Superficial wounds treated with daily sterile occlusive dressings.
5. Deep, infected, or devascularized wounds treated with debridement (surgical or enzymatic) and/or rotational muscle flaps when the wound is clean.

G. Musculoskeletal.

1. Development of contractures and spasticity may be slowed by aggressive range-of-motion exercises.
2. Heterotopic bone formation may be halted with etidronate sodium.

VIII. FUTURE DIRECTIONS

A. Many patients sustaining SCI die before reaching medical care. Those who survive to hospitalization who have or develop neurologic loss of function are then exposed to lifelong increased risks of complications: pneumonia, DVT, pressure ulceration, UTI, and loss of mobility with complete or near-complete disability. The costs associated with these problems are in billions of dollars per year. Limiting injury and complications and fostering neurologic recovery have become "the holy grail" of SCI care.

B. Neuroprotective agents under investigation.

1. Hypothermia.
   a. Experimental and clinical experience has shown that cooling protects neural tissues by decreasing its metabolic requirements and increasing its tolerance for decreased blood flow.
   b. Efficacy and safety of moderate hypothermia (32°C to 34°C) in clinical setting currently under investigation.
2. Minocycline.
   a. Reduces oligodendrocyte and microglial apoptosis.
   b. Clinical trial under way in Canada.
3. Riluzone, approved for use in patients with amyotrophic lateral sclerosis (ALS), is a sodium channel inhibitor that has neuroprotective properties. Because of encouraging animal studies, this drug is now in human multicenter trials.

C. Restorative/regenerative strategies.

1. Rho inhibitor: *Cethrin*: completed phase II human trials with encouraging results: improved ASIA scores in operated patients with SCI.
2. A number of investigations into the use of human mesenchymal or embryonic stem cells have been initiated internationally. No outcome data have been published to date.

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113 Abdominal Trauma

Ulises Torres

I. OVERVIEW

A. Background.

1. The abdomen is frequently injured after both blunt and penetrating trauma.
2. Abdominal trauma occurs in 20% of civilian injuries requiring surgery.
3. Half of all preventable deaths are related to suboptimal management of abdominal trauma.
4. Physical examination is often inadequate to identify or exclude intra-abdominal injuries (especially blunt trauma).
5. Multiple factors, including mechanism of injury, body region injured, hemodynamic and neurologic status, and associated injuries, influence the diagnostic approaches used and outcome of abdominal injuries.

B. Etiology.

1. Blunt trauma (the most common etiology) is caused by motor vehicle crashes (MVCs), motorcycle crashes, falls, and assaults and to pedestrians struck by vehicles.
2. Penetrating abdominal trauma is usually caused by gunshot or stab wounds.
3. Almost all causes are preventable.

C. Diagnosis.

1. History and physical examination.
   a. Trauma history: *A*llergies, *M*edications, *P*ast medical/surgical history, *L*ast meal, *E*vents surrounding the injury (AMPLE).
   b. Knowing the mechanism of the trauma is imperative in order to suspect the different intra-abdominal injuries.
   c. Suggestive clinical findings include abdominal wall contusions (seat-belt sign), pain, tenderness, or unexplained hypotension (Fig. 113-1).
   d. Peritoneal signs are absent in 40% of patients with significant abdominal injuries.
   e. Rectal examination for gross blood, bony fractures, tone, or urethral injury, although it is not a sensitive test.
   f. Foley catheterization is appropriate when no urethral injury is suspected: hematuria indicates injury to the bladder, ureters, or kidneys; in those cases, retrograde urethrogram is indicated.
   g. Physical findings are unreliable for patients with an abnormal sensorium secondary to head trauma, spinal cord injury, intoxication, or distracting pain from another source.

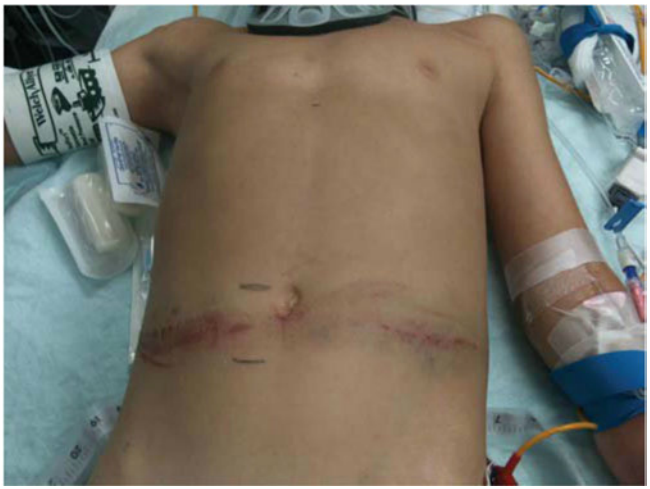

Figure 113-1. The seat belt sign, clearly demonstrated above, should trigger further investigation and observation.

2. Plain radiographs.
   a. Chest x-ray may reveal pneumoperitoneum; a gastric bubble or bowel in the chest is consistent with a ruptured diaphragm, and lower rib fractures suggest underlying liver or spleen injury.
   b. Abdominal x-ray has no role in the assessment of abdominal trauma with the exception of defining the trajectory of a projectile in order to choose the incision by the surgery team.
3. Computed tomography (CT).
   a. Abdomen and pelvic CT is the mainstay of diagnosis for abdominal and retroperitoneal injury in the hemodynamically stable patient.
   b. With intravenous contrast material, CT can detect arterial contrast extravasation.
   c. Oral contrast is not necessary for trauma CT; does not increase sensitivity.
   d. Sensitivity rates are between 92% and 97.6% and specificity rates as high as 98.7%. Negative predictive value up to 99%.
   e. Unreliable in identifying hollow visceral injuries.
   f. Contraindicated in hemodynamically unstable patients (who would benefit from intervention, rather than diagnostic testing).
4. Focused assessment with sonography for trauma (FAST).
   a. Includes four areas of examination:
      i. Right upper quadrant: Morrison pouch between the right kidney and liver.
      ii. Left upper quadrant: between the left kidney and spleen.
      iii. Subxiphoid: pericardium (alternatively transsternal).
      iv. Suprapubic: perivesicular spaces.

5. FAST has mostly replaced diagnostic peritoneal lavage (DPL) and gained acceptance in the evaluation of abdominal trauma, especially in the hemodynamically unstable patient; primarily used to detect occult intra-abdominal blood. DPL and/or FAST usage depends on the skill and experience of the clinician.
   a. FAST is accurate in detecting intra-abdominal blood (94% to 96%) in experienced hands.
   b. Advantages include being rapid, portable, and noninvasive; disadvantages include low specificity for source of hemorrhage and high operator dependence.
   c. A normal FAST does not exclude injuries of hollow viscus and retroperitoneal injuries.
   d. With appropriate training, FAST can be effectively performed by nonradiologists.
   e. The FAST examination can be easily used at the bedside at any time after the initial trauma.
6. Laparoscopy.
   a. Use of diagnostic laparoscopy in blunt abdominal trauma is a developing field.
   b. Difficult to adequately examine small bowel and retroperitoneum.
   c. Accurate in determining peritoneal or diaphragmatic penetration from stab wounds or tangential gunshot wounds.
7. Nonoperative management (NOM) and serial examinations.
   a. Can be used for some blunt trauma and superficial stab wound patients with normal mental status and hemodynamic stability.

D. Treatment.

1. For blunt abdominal trauma, treatment is dictated by the specific injuries present.
2. Operative exploration is required in all patients with anterior abdominal gunshot wounds because visceral injury is present in >90% of cases.
3. For stab wounds, exploration is necessary in the presence of peritoneal signs, hemodynamic instability, evisceration of abdominal contents, or confirmed peritoneal penetration.
4. Unexplained hypotension with physical signs of abdominal trauma may warrant exploration.

II. SPECIFIC INJURIES

A. Liver and porta hepatis.

1. **Background.**
   a. The liver is the most commonly injured organ in blunt abdominal trauma.
   b. Spontaneous hemostasis is observed in >50% of small hepatic lacerations at the time of laparotomy.
   c. Most liver injuries heal without intervention.
   d. Overall mortality rate ranges from 8% to 10% depending on the number of associated injuries and injury severity.

e. Injuries are graded from I (minor) to V (severe), ranging from minor tears to major lobar disruptions and avulsion from the inferior vena cava.
f. Hemobilia results from erosion of an injured blood vessel into a biliary duct.
g. Traumatic injuries to the porta hepatis are uncommon. It is more common with penetrating trauma and has a 50% mortality rate from hemorrhage.

2. **Diagnosis.**
   a. Abdominal CT is the most sensitive and specific study in identifying and assessing the severity of injury. FAST or DPL is used in hemodynamically unstable patients although they will not be specific for liver injury.

3. **Treatment.**
   a. NOM is the treatment of choice in hemodynamically stable patients.
   b. Angiography with embolization can be used to stop arterial hemorrhage when contrast extravasation is seen on CT.
   c. Surgery is indicated for patients who are hemodynamically unstable, develop peritonitis, or require continuous blood transfusions.
      i. Simple lacerations are managed by direct pressure, suture repair, electrocautery, argon beam coagulation, and topical hemostatic agents.
      ii. Hepatic packing is the preferred initial technique for significant injuries with hemorrhage.
      iii. Compression of the portal triad (Pringle maneuver) is effective if the aforementioned techniques fail; this is a temporizing measure only.
      iv. In cases of hepatic venous or retrohepatic inferior vena caval injuries, total hepatic exclusion or atriocaval shunts are options. Damage control techniques (abdominal packing and temporary abdominal closure) should receive strong consideration in the face of such injuries.
   d. Gallbladder injuries are treated with cholecystectomy.
   e. Injuries to extrahepatic bile ducts require primary repair or anastomosis to the bowel.
   f. Bile leaks are detected clinically or with hepatobiliary iminodiacetic acid (HIDA) scan posttrauma day 2 to 3, treated with closed drainage either at surgery or percutaneously with the aid of CT or ultrasound and stenting via endoscopic retrograde cholnagiopancreaticography (ERCP).

4. **Complications.**
   a. Bleeding, hemobilia, bile leak, and intra-abdominal abscess.
   b. Bile leak occurs in 25% of patients with major hepatic injuries.
   c. Abscesses occur in 10% of patients with liver injuries; likelihood of infection increases with grade of injury, number of transfusions, use of sump drains, concomitant bowel injury, and perihepatic packing.

B. Spleen.

1. **Background.**
   a. Commonly injured in both blunt and penetrating trauma.
   b. May result from a blow, fall, or sports injury involving the left chest, flank, or upper abdomen; side impact MVC is a common cause.
   c. Injuries graded from I (minimal) to V (most severe).

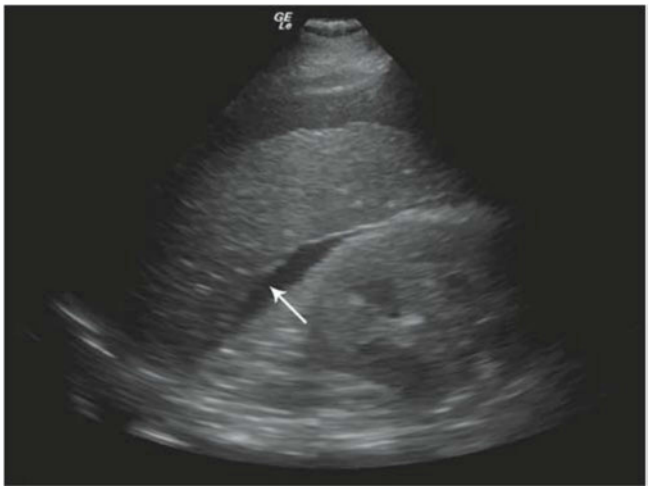

Figure 113-2. Fluid (*arrow*) in the liver–kidney interface.

2. **Diagnosis.**
   - **a.** FAST or DPL is used in hemodynamically unstable patients (Fig. 113-2).
   - **b.** CT with intravenous contrast (oral contrast is unnecessary) is the most sensitive and specific study for identifying and grading splenic injuries.
3. **Treatment.**
   - **a.** NOM of blunt splenic injuries is the treatment of choice in hemodynamically stable patients.
   - **b.** Surgery is indicated for hemodynamically unstable patients.
   - **c.** NOM of high-grade injuries is preferably done at level I trauma centers with the experience and intensive resources required.
   - **d.** Patients undergoing NOM should be closely monitored, usually in an intensive care unit, for at least 48 hours with attention to vital signs, serial hematocrits, and serial abdominal examinations and bed rest.
   - **e.** Surgery or angiography with embolization can be considered for stable patients with extravasation of intravenous contrast on CT and may increase the success rate of NOM.
   - **f.** The success rate of NOM is approximately 90%, but varies with the grade of injury.
   - **g.** Surgical treatment varies depending on the severity of injury, presence of shock, and associated injuries.
4. **Complications.**
   - **a.** Recurrent or delayed bleeding.
   - **b.** Subphrenic abscess: This can be present also after embolization.
   - **c.** Left pleural effusion secondary to sympathetic response.

d. Overwhelming postsplenectomy infection (OPSI).
  i. Asplenic patients are at increased risk for sudden and, often, lethal systemic bacterial infection.
  ii. OPSI is usually caused by encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*).
  iii. The incidence of OPSI is 0.6% in children and 0.3% or less in adults after splenectomy for trauma; there is a higher incidence after splenectomy for hematologic disease.
  iv. After splenectomy, vaccination against the above three organisms is given before discharge or 2 weeks postoperatively.
  v. Use of prophylactic antibiotics in asplenic patients is controversial, but is often used in young children.

C. Kidneys.

1. Background.

a. Approximately 10% of all abdominal traumas involve the kidneys.
b. Graded from I (minimal) to V (most severe).
c. Retroperitoneal, so may not be identified with physical examination, DPL, or FAST.
d. Gerota fascia encapsulates the kidney and will often tamponade a hematoma.

2. Diagnosis.

a. CT with intravenous contrast is the study of choice.
b. High-grade renal injuries may be seen on FAST examination.
c. Intravenous pyelogram (IVP) has no indication in trauma outside of the operating room; replaced by CT.
d. Although urinary catheter is helpful in the diagnosis, the absence of blood in the urine does not rule out an injury to the genitourinary tract.

3. Treatment.

a. NOM is the treatment of choice for hemodynamically stable patients.
b. A completely devascularized, nonfunctioning kidney should be managed nonoperatively initially.
c. Absolute indications for operative repair or nephrectomy include exsanguination, expanding or pulsatile retroperitoneal hematoma, or continued instability.

4. Complications.

a. Urinoma: Attention to early detection is important due to the prolonged ileus that usually accompanies this entity.
b. Acute renal insufficiency (unlikely with one kidney injury).
c. Urinary tract infection or infected urinoma.
d. Perinephric abscess.
e. Hypertension (a rare, late complication in some severe injuries).

D. Diaphragm.

1. Background.

a. Patients sustaining penetrating injuries between the nipple and the costal margin should be investigated to rule out diaphragmatic injury.
b. Following penetrating trauma, injury to the diaphragm involves both sides equally; in blunt trauma, the left side is more frequently injured.

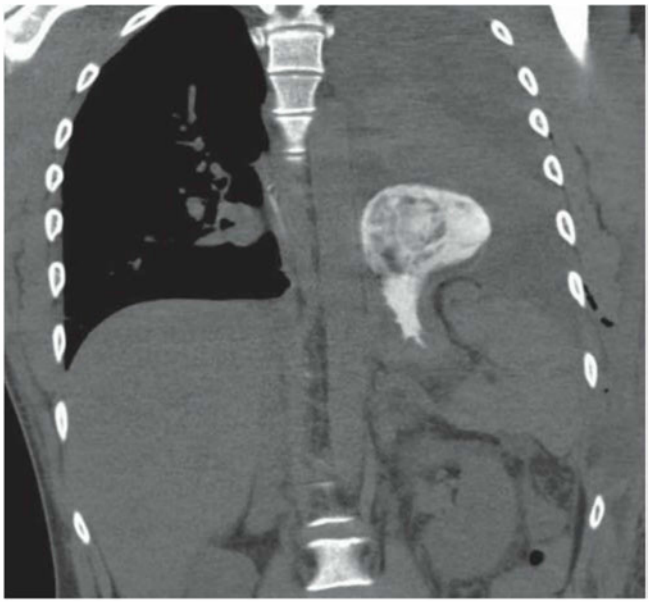

Figure 113-3. Left diaphragmatic rupture; stomach in chest.

2. **Diagnosis.**
   a. Requires a high index of suspicion; often clinically occult.
   b. Radiologic modalities, including CT, are usually insufficient to exclude this injury.
   c. Chest radiography is abnormal in 85% of cases, yet diagnostic in only 27% of cases. Placement of an NGT prior to the CXR is helpful in the diagnosis of the most frequent type of rupture, which is the left side (Fig. 113-3).
   d. If the diagnosis is uncertain, further evaluation is warranted with laparoscopy, thoracoscopy, or exploratory laparotomy.
3. **Treatment.**
   a. Almost all diaphragm injuries require repair due to risk of enlargement over time with continuous movement of the diaphragm.
   b. Suture repair to create watertight closure.
   c. Larger defects may require use of prosthetic material.
4. **Complications.**
   a. Delayed or missed diagnosis.
      i. Early recognition is critical, since the mortality of an untreated injury and subsequent bowel strangulation is approximately 30%.

E. Small intestine.

1. **Background.**
   a. Most commonly injured organ in penetrating abdominal trauma.
   b. Blunt small bowel injury (SBI) is extremely rare, with an incidence of 1.2% of all trauma admissions; one-fourth of all SBI are perforated.

2. **Diagnosis.**
   a. Physical findings may be delayed until the patient is septic or has peritonitis.
   b. Presence of abdominal wall bruising, especially from a seat belt (Fig. 113-1), should raise suspicion of SBI.
   c. Lumbar Chance fractures are associated with SBI (as well as pancreatic and duodenal injuries).
   d. Findings of SBI on CT may include free air, free fluid without solid organ injury, thickened bowel wall, and mesenteric hematoma. Aside from free air, all other CT findings are insensitive and nonspecific for SBI.
      i. Fourteen percent of patients with perforated SBI have a "negative" CT.
      ii. Oral contrast leak is seen on CT in only 2.9% of perforated SBI.
   e. Peritonitis or increasing abdominal tenderness mandates exploration.
3. **Treatment.**
   a. Operative technique depends on the severity of injury and can range from simple repair to resection with anastomosis.
   b. If there is concern for vascular sufficiency, a second laparotomy after 24 to 48 hours may be indicated to reevaluate bowel viability.
4. **Complications.**
   a. Intra-abdominal abscesses.
   b. Sepsis, especially if treatment is delayed.
   c. Anastomotic leak.
   d. Bowel ischemia/necrosis.

SUGGESTED READINGS

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114 Burns

Philip Fidler and James C. Jeng

I. GENERAL PRINCIPLES

A. Definition.

A burn is a tissue injury resulting from excessive exposure to thermal, chemical, electrical, or radioactive agents.

1. Epidermis serves as a barrier to fluid and heat loss and barrier to infection.
2. Dermis: provides the overall structural integrity of the skin and maintains the epidermis.

II. CLASSIFICATION

A. It is essential to distinguish between second-degree and third-degree injuries of the dermis, as the latter require operative intervention.

1. Superficial (first degree) burns involve epidermis only.
   a. Erythema; blanch when touched; do not blister.
2. Partial (second degree) burns.
   a. Involve epidermis and part of dermis. Divided into superficial and deep.
   b. Superficial—blistering, weeping, pink, and painful skin; will reepithelialize.
   c. Deep—paler; do not blanch; some sensation remains; take longer to reepithelialize.
3. Full-thickness epidermis, dermis, and even subcutaneous fat, muscle, bone:
   a. Pale, leathery, and insensate skin.
4. Injury can progress over time, and partial-thickness burns can convert to full thickness.

III. EPIDEMIOLOGY

A. Risk factors.

1. Infants and elderly are more frequently affected.
2. Cognitive impairment.
   a. Behavioral disorders.
   b. Impairment from alcohol or drug effects.

B. Prognosis markedly improved in the last 25 years.

1. Lethal dose 50 (LD50) for young adults is a 90% total body surface area (TBSA) burn, and the LD50 for the elderly is a 40% TBSA burn.
2. Shift toward, "early" (within 5 days), operative excision as it was realized that burned tissue drives burn shock.

3. Diminution of burn wound sepsis and advances in critical care borrowed from all disciplines have contributed to improved outcomes for young patients and in the elderly.
4. Clinical data points predicting mortality (mortality rates of 90% when all three are present and 33% when two factors are present):
   a. Age older than 60 years.
   b. TBSA burned ≥40%.
   c. Inhalational injury.

IV. PATHOPHYSIOLOGY

A. Burn shock.

1. Occurs in ≥20% TBSA burns.
2. Due to elements of distributive and hypovolemic shock:
   a. Massive insensible evaporative fluid loss from burn wounds.
   b. Intravascular volume depletion from interstitial edema in both burned and unburned tissue.
   c. Forces central shunting of blood to improve core perfusion, but deprives the burn wound.

B. Massive edema.

1. Occurs in burn wound and nonburned tissue.
   a. Results from increased vascular permeability driven by vasoactive mediators, including kinins, serotonin, histamine, prostaglandins, and oxygen radicals.
   b. Decreased oncotic pressure.

C. Cardiovascular response.

1. Decreased preload.
2. First 48 hours, decreased cardiac output (myocardial depressant factors likely gut derived).
   a. Decreased compliance and contractility, particularly after inhalational injury.
3. After first 48 hours develop hyperdynamic cardiac state that may last for weeks.

D. Infection—increased susceptibility.

1. Lungs.
   a. Pneumonia.
   b. Tracheobronchitis.
2. Burn wounds:
   a. *Staphylococcus aureus* and *Streptococcus* first week, followed by *Pseudomonas, Klebsiella,* and *Acinetobacter*; Late: Fungus.
3. Central line sites.
4. Urinary tract.
5. Gut.
   a. If not fed, may be source of translocation of bacteria and source of sepsis.
   b. Enteral feedings can prevent gut atrophy and immunoenhancing nutritional regimens; especially those with glutamine further resist atrophy and may afford better outcomes.

V. DIAGNOSIS

A. History.

1. The heat source and circumstances of the injury.
2. When the burn injury occurs coincidentally with blunt trauma.
a. Life-threatening injuries take precedence in early management.
b. Burn skin management is secondary.
3. If burn occurs in closed space—expect inhalation injury.

B. Electrical injuries.

1. High voltage.
a. May present with little injury to the skin, but significant injuries to the muscle, vasculature, and bone.
b. Cardiac standstill/arrhythmias in first 24 hours.
2. Low voltage.
a. Present as thermal burns, with injuries to the tissue from the outside to inside.
b. Ventricular fibrillation.

VI. PHYSICAL EXAMINATION

A. Multiples of the number 9 ("the rule of nines") to assess surface area of partial- and full-thickness burns.
B. Lund-Browder scale (Fig. 114-1).
C. For noncontiguous injuries, the palmar surface of the patient's hand can be used to estimate 1% TBSA.

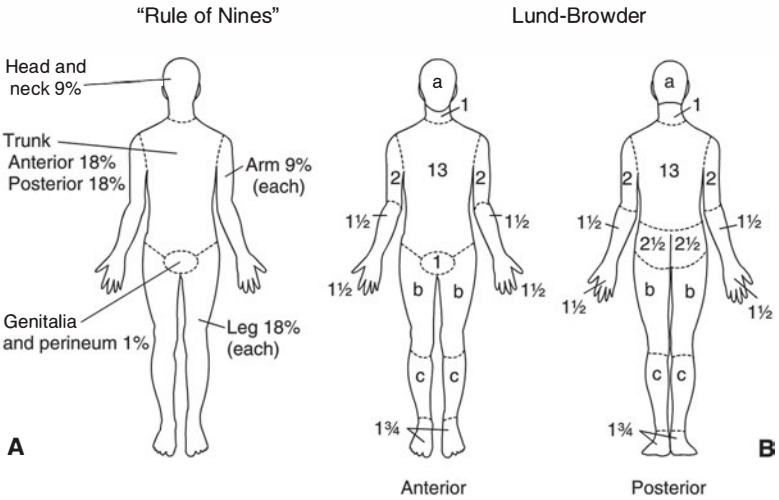
VII. TREATMENT

A. Airway management.

1. Consider early intubation for
a. Inhalational injury (stridor, hoarseness).
b. TBSA > 40% as massive soft tissue edema can occur during resuscitation.

B. Burn shock.

1. Ideal resuscitation perfuses the partial-thickness injury and optimizes organ function.
2. Underperfusion deprives the wound of nutrient delivery and gas exchange, leading to full-thickness conversion.
3. Excessive resuscitation leads to tissue edema, pulmonary edema, abdominal compartment syndrome, and extremity compartment syndrome.
4. Central venous access is generally necessary and preferably placed through uninvolved tissue.
5. Resuscitative regimens.
a. TBSA burned and weight-guide fluid management.
b. No evidence-based level-one data for resuscitative fluids use.



Relative percentage of body surface areas (% BSA) affected by growth

	0 yr	1 yr	5 yr	10 yr	15 yr
a— ½ of head	9½	8½	6½	5½	4½
b— ½ of 1 thigh	2¾	3¾	4	4¼	4½
c— ½ of 1 lower leg	2½	2½	2¾	3	3¼

Figure 114-1. **A:** Rule of Nines. **B:** Lund-Browder scale.

i. Lactated Ringer's most commonly used. Normal saline in large volumes causes hyperchloremic acidosis and should be avoided (Table 114-1).

c. Colloid use remains controversial and serves as adjunct to crystalloid.

6. End points of resuscitation.

a. Urine output.

i. Primary end point for majority of burn centers.

ii. Goals: adult 0.5 mL/kg/h, children 1 mL/kg/h.

iii. Adjust fluid administration hour to hour based on urine output.

b. Other end points of resuscitation—base deficit, lactate, and stroke volume variability.

C. Metabolism and nutrition.

1. Metabolism.

a. Insensible fluid and protein losses from burn wounds are extreme and may result in hyperthermia initially.

b. As vasomotor autoregulation diminishes, significant evaporative heat loss occurs.

c. Keep the patients' room temperature >90°F.

d. Increased muscle proteolysis, lipolysis, and gluconeogenesis occur.

e. Hyperglycemia is common and may exacerbate muscle wasting.

f. Glucose control is essential with insulin drip.

TABLE 114-1 Parkland and Modified Brooke Formulas

Parkland formula	Total fluids for 24 h =	
	Ringer lactate	4 mL × kg × %BSA
Modified Brooke formula	Total fluids for 24 h =	
	Ringer lactate	1.5 mL × kg × %BSA
	Plasma	0.5 mL × kg × %BSA
	D5W	2,000 mL

Example: A 70-kg man with a 50% TBSA burn would therefore have a total deficit of 14 L (4 mL × 70 kg × 50% BSA = 14,000) in 24 h. Half the 24-h deficit should be repleted in the first 8 h, due to the high risk of hypovolemic shock early in the course. In this example, that is 7 L within the first 8 h or a rate of 875 mL/h for the first 8 h. It is important to note that this recommendation starts at the estimated time of injury, not simply the time care is rendered. The rate would subsequently be decreased to *438 mL/h* for the next 16 h.
BSA, body surface area; D5W, dextrose 5% in water.

g. Hypermetabolic response that occurs after a thermal injury is greater than that observed after any other form of trauma or sepsis.
  i. Protein catabolism is compounded by insensible losses through the wound bed and leaking into the interstitium, resulting in severe hypoproteinemia.

2. Nutrition.
  a. Ideally, enteral nutrition should be started the day of the injury and can serve to provide volume and calories.
  b. Caloric need is equal to two to three times normal basal energy expenditure and requires minimum of 2 g/kg protein per day.
  c. Enteral nutrition is preferred, and total parenteral nutrition (TPN) is used only for patients who do not tolerate enteral feedings.
  d. Anabolic enhancement.
    i. Recombinant human growth hormone.
      (a) Caution: may cause hyperglycemia.
    ii. Oxandrolone: given enterally 10 mg bid.
    iii. Propanolol: titrate to reduce heart rate by 20%.

C. Infection.

1. Multiple defects in burn patients' immune system predispose them to an increased risk of infection.
2. Burn wound sepsis.
  a. Prevention of
    i. Topical antimicrobials (e.g., silver sulfadiazine or mafenide acetate).
      (a) Mafenide acetate penetrates eschar and is most effective against gram-negative organisms but can cause metabolic acidosis because it is a carbonic anhydrase inhibitor.
    ii. Local wound care.
  b. Treatment.
    i. Urgent surgical excision and tissue coverage with autograft, skin substitute, or topical antibiotics when burn wound sepsis is suspected.

D. Inhalation/respiratory injury.

1. Restrictive respiratory failure secondary to burn eschar involving the torso requires urgent escharotomy.

2. Inhalation injury.

a. Airway management as always is paramount.

i. Observe for signs of upper airway obstruction, secondary to edema, which develops hours after the initial injury.

ii. Stridor is an indication for urgent placement of an endotracheal (ET) tube of sufficient caliber to permit bronchoscopy in this setting.

iii. Immediate life-threatening exposures.

(a) Carbon monoxide.

(1) Lethal level >60% CO Hgb.

(2) FIO_2 100% until normal level.

(b) Hydrogen cyanide (CN^-).

(1) Lethal level in serum ≥1 μg/mL.

(2) Inhibits cytochrome oxidase.

(3) Consider sodium thiosulfate.

b. Inhalation of toxic combustants can cause a severe inflammatory response in the bronchial pulmonary tree and systemically.

i. Endobronchial and interstitial edema.

ii. Mucociliary dysfunction.

iii. Alveolar disruption.

iv. Functional pulmonary shunting.

v. Decreased lung compliance.

vi. Endobronchial sloughing.

(a) Combines with exudates + fibrin = casts with increased bacterial growth and obstruction of airways.

vii. Neutrophils invade in alveolar spaces through the pulmonary vasculature release enzymes and likely contribute to O_2 free radical production, promoting the inflammatory cascade and local injury.

viii. Mortality is greatly increased when matched to burn injuries of like size without inhalational injury.

ix. Upper airway assessment should be carried out before extubation by deflating cuff and noting an air leak. It may not be safe to extubate if no air leak is audible!

c. Shock state can be more severe in the presence of inhalational injury, often requiring up to 50% more fluid to meet the urine output end points of resuscitation.

E. Chemical injury.

1. Acids.

a. Burn by coagulation necrosis creating an eschar that limits deeper penetration.

b. Hydrofluoric acid burns carry the unique concern of calcium and magnesium chelation and risk cardiac arrest secondary to severe hypocalcemia and hypomagnesemia.

i. Intra-arterial infusion of calcium gluconate has been met with some success and may limit digital ischemia.

ii. Calcium gluconate slurry may be massaged into the exposed area to potentiate systemic absorption.
iii. Carefully monitor electrocardiogram (ECG).

2. Alkali.
   a. Burn by causing liquefaction necrosis in the subcutaneous fat, creating vascular thrombosis and subsequent dermal ischemia.

F. Electrical injury.

1. Life-threatening problems include dysrhythmias.
2. Spinal cord injury.
   a. Direct nerve/cord damage.
   b. Tetany resulting in spinal column fracture and cord injury.
   c. May result in impaired respiratory function depending on the level of injury.
3. Cutaneous lesions.
   a. May be subtle, and efforts should be made to find entrance and exit lesions, as these will direct the practitioner to focus on the intervening tissues.
4. Compartment syndromes.
   a. Myonecrosis is common, particularly in the upper extremities.
   b. Myonecrosis puts the kidneys at risk for myoglobinuric renal failure.
      i. Elevations of creatinine phosphokinase (CPK) into the tens of thousands are often present, and maintaining a urine output of 100 mL/hour or greater in adults reduces the risk of renal failure.
      ii. Mannitol may be added once resuscitation is well under way.
      iii. Alkalinizing the urine is advocated by some.
      iv. Maintain urine output at 100 mL/hour in adults.
      v. Consider monitoring the CPK for several days to assess the amount of muscle damage and recovery; with continued elevations suggesting need for further debridement.
   c. Fasciotomy for elevated compartment pressures.
   d. Debridement of nonviable or necrotic muscle and/or other tissue.
5. Fluid resuscitation must be initiated quickly, with higher volumes than anticipated due to underlying tissue injury.

G. Pain.

1. Rationale.
   a. On a scale of 1–10, most burns are rated at a 10.
   b. Pain control leads to
      i. Patient comfort.
      ii. Decreased catabolism, cardiovascular stress.
      iii. Reduced risk of posttraumatic stress disorder.
2. Management.
   a. Simultaneous drips of narcotic and benzodiazepines.
   b. Anticipate higher doses than are usual for other clinical settings.
   c. It is not prudent to reduce these medications for frequent neurologic assessment.

d. Once the patient's burn wounds have been managed adequately, a stepwise weaning of these agents is done to permit ventilator weaning and to avoid withdrawal.

VIII. COMPLICATIONS

A. Eschar formation.

1. Escharotomy.
- **a.** *Particularly* for circumferential chest eschar to optimize oxygenation/ventilation.
- **b.** For limbs to prevent compartment syndromes.

2. Burn wound sepsis.
- **a.** Early excision.
  - **i.** Reduced risk of this complication.
  - **ii.** Nonetheless, loss of skin barrier and immune suppression may still not totally prevent burn wound sepsis.
- **b.** Signs.
  - **i.** Diffuse or focal discoloration of the burn.
  - **ii.** Purulent fluid from the wound.
  - **iii.** Early eschar separation.
  - **iv.** Confirm by biopsy of wound.
- **c.** Treatment.
  - **i.** Immediate treatment or *systemic sepsis will occur*.
  - **ii.** Total excision of the infected wound.
  - **iii.** Systemic antibiotics covering the infective microbes.

3. Abdominal compartment syndrome.
- **a.** Leads to renal failure, respiratory failure, and bowel ischemia.
- **b.** Urinary bladder pressure measurement protocol.
- **c.** Provides an indirect measure of abdominal pressure.
- **d.** Levels ≥20 cm H_2O pressure suggest abdominal hypertension, and ≥30 cm H_2O is generally accepted as requiring operative intervention, celiotomy, and leaving the abdominal compartment open.

4. Pneumonia.
- **a.** Increased risk because of immune compromise, immobility, and impaired secretion clearance.
- **b.** More frequent with inhalational injury.
- **c.** Incidence increases with the burn area.
- **d.** Prevention.
  - **i.** Good pulmonary toilet.
  - **ii.** Limit aspiration by keeping head of bed at 30 degrees.
  - **iii.** If on ventilator, lung-protective ventilator management.
  - **iv.** Frequent surveillance.
  - **v.** Prophylactic antibiotics are not recommended.
- **e.** Treatment.
  - **i.** Initial empiric therapy based on local biograms followed by culture-directed therapy based on the sensitivities of the isolated organisms.

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115 Thoracic Trauma

Hani Seoudi and Bruce J. Simon

I. GENERAL PRINCIPLES

Chest injuries cause one of every four trauma deaths in North America. Multiple life-threatening injuries can result from thoracic trauma and therefore should be sought during the primary trauma survey.

II. ETIOLOGY

Motor vehicle crashes, falls, and penetrating wounds are the principal causes.

III. DIAGNOSIS

A. Tension pneumothorax. Air enters the pleural space but does not leave because of a flap valve effect in the injured lung or from an open (sucking) chest wound. As a result, positive intrapleural pressure occurs, the ipsilateral lung collapses, and the mediastinum is pushed toward the contralateral lung. This results in hypotension and tachycardia due to impaired venous return.

B. Massive hemothorax. This represents rapid accumulation of >1,500 mL of blood within the pleural space and manifests as hemorrhagic hypovolemia in addition to respiratory compromise.

C. Flail chest. This indicates that a segment of chest wall has lost bony continuity with the remainder of the chest due to fracture of three or more adjacent ribs in more than one location unilaterally or bilaterally. This results in paradoxical movement of the flail segment during respiration. The morbidity of this condition is primarily due to the pain and associated severe pulmonary contusion.

D. Cardiac tamponade. This may result from either blunt or penetrating trauma. Acute accumulation of relatively small amounts of blood can result in tamponade pathophysiology. Clinical findings include hypotension, tachycardia, muffled heart sounds, distended neck veins, and pulsus paradoxus. Detection is by trauma ultrasound exam ("extended FAST exam").

E. Major airway injury. This injury is characterized by stridor and subcutaneous emphysema. Endotracheal intubation can be very difficult, and failed attempts at intubation can further compromise airway function. It is recommended that an emergency tracheostomy rather than cricothyroidotomy be performed. Urgent operative repair is needed.

F. Penetrating chest injury. Penetrating injuries in addition to the stated problems may also result in bronchovenous fistula, whereby air flows from the injured bronchus into one of the pulmonary veins, resulting in massive

air embolism. This condition can have a delayed presentation and appear when positive pressure ventilation is initiated. The condition is rapidly fatal and requires immediate thoracotomy.

IV. IMMEDIATE LIFESAVING INTERVENTIONS

A. Endotracheal intubation. Intubation is indicated when the airway is compromised by direct trauma, aspiration of blood/gastric contents, or a depressed level of consciousness. Orotracheal intubation is the preferred method.

B. Cricothyroidotomy. Dividing the cricothyroid membrane provides a much quicker surgical access to the airway compared to tracheostomy. Tracheostomy is usually not performed in a lifesaving situation.

C. Needle decompression or tube thoracostomy. Immediately on identification of a tension pneumothorax, a needle thoracostomy should be performed. This should be followed by a tube thoracostomy as quickly as possible.

D. Thoracotomy. It is recommended that a thoracotomy be performed if the initial drainage from the tube thoracostomy is 1,500 mL or greater or when the hourly output is >250 mL for several hours. Resuscitative thoracotomy, also known as *emergency department thoracotomy*, is performed on pulseless victims of penetrating trauma who have other signs of life. Generally, a resuscitative thoracotomy is not performed on blunt trauma victims who are without vital signs. The overall success rate of this procedure is low.

V. DIAGNOSTIC STUDIES

A. Chest radiograph is the first imaging study performed for the trauma patient after the primary survey. However, in many centers extended FAST (eFAST) ultrasound of the chest is immediately performed on patient arrival to the trauma bay to assess for pneumothorax.

B. eFAST exam is done of the pericardium to rule out hemopericardium.

C. Computed tomography (CT). High-speed helical CT scanners permit rapid evaluation of chest injuries and are accurate for diagnosing lung contusions and occult hemopneumothorax. Modern CT scanners are highly accurate in diagnosing blunt aortic injury.

D. Angiography. Aortography remains the gold standard for making the diagnosis of blunt aortic injury but is gradually being supplanted by thin-slice CT angiography.

VI. TREATMENT

A. Chest wall and pleural cavity injury.

1. Rib fractures: Rib fractures need only be treated symptomatically. Pain control can be challenging depending on the number and extent of the fractures. A thoracic epidural catheter or unilateral paravertebral catheter is useful for pain control in older individuals and those with multiple rib fractures.

2. Flail chest: This injury is particularly challenging because patients frequently go into respiratory failure due to the severe pain and hypoxia due to the underlying pulmonary contusion. Mechanical ventilation is usually necessary. Repair is sometimes done, but the benefit remains controversial.
3. Sternal fracture. Symptomatic treatment for this injury is appropriate.
4. Pneumothorax.
   a. Pneumothorax is generally treated with tube thoracostomy. A very small pneumothorax may be observed if the patient is not symptomatic. Open pneumothorax: the initial management includes immediately applying an occlusive dressing over the wound and insertion of a chest tube; operative intervention is urgently needed when the assessment for other life-threatening injuries has been completed.

B. Lung.

1. Pulmonary contusion. Treatment is supportive with supplemental oxygen. Mechanical ventilation is necessary if there is severe hypoxia.
2. Acute respiratory distress syndrome (ARDS). ARDS is a syndrome of diffuse inflammatory reaction in the lung as part of a systemic inflammatory response. It may occur following multiple traumas, sepsis, massive blood transfusions, and many other causes (see Chapter 40 for more details).

C. Trachea and major bronchial injuries. After securing an airway, these injuries require immediate operative intervention. When patients are otherwise unstable, repair can often be deferred if respiratory function is acceptable and the air leak is not excessive.

D. Heart and great vessels.

1. Blunt cardiac injury. This term encompasses a variety of injuries, including myocardial contusion, rupture of a cardiac chamber or septum, and valve disruption.
   a. Treatment for myocardial contusion requires cardiac monitoring and supportive care.
   b. Treatment of chamber, septal, or valve injury often requires urgent surgical repair.
2. Blunt aortic injury. Most patients with this injury die before reaching the hospital. Approximately half of those who reach the hospital will have a free rupture within the first 24 hours. Therefore, urgent surgical repair is indicated. Nonoperative management: treatment principles are similar to nonoperative management of aortic dissection, that is, β-blockade and antihypertensives; endovascular stent grafts are now being used much more frequently, particularly for the poor-risk or elderly patient.

E. Traumatic asphyxia. When a trauma patient is diagnosed with this problem, treatment is supportive after establishing an airway and ventilation. Elevated intracranial pressure should be ruled out by CT scan if mental status is altered.

F. Esophageal rupture. Surgical treatment is indicated to avert mediastinal and/or pleural sepsis.

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116 Compartment Syndromes Associated with Musculoskeletal Trauma

Timothy A. Emhoff

I. TRAUMATIC COMPARTMENT SYNDROMES

A. General principles.

1. Any anatomic structure or external device that limits the ability of tissues to swell can cause compartment syndrome.
2. Compartment syndromes due to trauma are typically described in extremities (leg, arm, thigh), abdomen (see Chapter 102), face (eye), and head (see Chapter 111).
3. Anatomically, extremity compartments are formed by fascial layers surrounding muscle groups.
4. As compartment pressure increases, nerves, followed by muscles, lose function (if treatment is delayed).
5. Extremity compartment syndrome can occur in the calf, thigh, buttock, forearm, arm, hand, or foot. The most frequent compartment affected is the anterior compartment of the calf.
6. With trauma to the face, retrobulbar hemorrhage or edema may jeopardize the optic nerve.
7. In closed head injury, unrelieved elevated intracranial pressures may be amenable to decompressive craniectomy before permanent brain damage occurs.

B. Etiology.

1. Extremity compartment syndrome: crush, ischemia, arterial injury, vascular ligation (including vena cava, common iliac, common femoral, or popliteal veins), fracture (open or closed), direct blunt trauma (with hematoma or edema), prolonged external pressure, electrical injury, or contrast injection/extravasation.
2. Secondary extremity/ocular compartment syndrome: hypotension and/or massive volume resuscitation leads to whole-body tissue edema, including the muscles of the various compartments. This may be the result of massive burns or other large physiologic insults, and is part of the postresuscitation systemic inflammatory response syndrome (SIRS).

C. Pathophysiology.

1. Injury and/or resuscitation causes a hematoma and/or edema of the muscles.
2. In the face of a fixed compartment volume, pressure increase follows muscle edema.
3. At some point, pressure in the compartment exceeds capillary perfusion pressure (approximately 30 mm Hg), and the capillaries collapse.
4. Tissue ischemia results in nerve (initial) and muscle damage (late).

D. Diagnosis.

1. High index of suspicion is the key, especially in the neurologically compromised patient.
2. Lower extremity clinical examination.
   - **a.** Four compartments:
     - **i.** Anterior: peroneal nerve: dorsiflex foot and toes.
     - **ii.** Posterior: plantar flex the foot.
     - **iii.** Lateral: plantar flex the foot.
     - **iv.** Deep posterior: inverts foot, flexes toes.
   - **b.** Tense or tight compartments to touch (compare right to left).
   - **c.** Pain disproportionate to associated injury.
     - **i.** Critical mistake is to treat with more pain medication.
   - **d.** Increased pain with passive muscle stretch (classically for anterior calf compartment: dorsiflexion of the great toe).
   - **e.** Hypesthesia and/or muscle weakness: test for all compartments.
   - **f.** Pallor: sluggish capillary refill in the skin/nail bed.
   - **g.** Distal pulses remain intact unless a proximal arterial injury is the reason for the compartment syndrome.
     - **i.** Critical mistake is to think that diagnosis of compartment syndrome is dependent on pulse loss.
   - **h.** Direct measurement.
     - **i.** Arterial line setup and 16-gauge needle.
     - **ii.** Commercial device with direct readout (Stryker Orthopedics: www.stryker.com).
     - **iii.** Less than 20 mm Hg is usually not problematic; 20 to 30 requires expert interpretation of the clinical picture; >30 is clearly abnormal and requires fasciotomy.
3. Upper extremity clinical exam.
   - **a.** Three compartments:
     - **i.** Volar: (includes carpal tunnel): median, ulnar, and anterior interosseous nerves (flexor muscles).
     - **ii.** Dorsal: posterior interosseous nerve (extensor muscles).
     - **iii.** Mobile wad: radial nerve.
4. Ocular clinical exam.
   - **a.** Proptosis.
   - **b.** Computed tomography: blood, fluid, bone forcing eye forward, stretching optic nerve ("balloon-on-a-string").
   - **c.** Physical exam (PE): firm globe to touch. (Note: measured intraocular pressure may NOT reflect increased pressure behind the globe, which threatens the optic nerve and retinal perfusion.)

d. Sluggish papillary response (direct and indirect).
e. "Pale" optic nerve on funduscopic exam.
f. Awake patient: blurred vision (progressive).
g. Direct measurement: not done.

E. Treatment.

1. Extremity compartment syndrome.
a. The first step is always to remove constricting wraps or dressings and to remove or bivalve any cast as these devices may cause or hide compartment syndrome.
b. Fasciotomy: within 6 hours of onset; 3 to 4 hours if high compartment pressures are associated with severe blood loss, hypoperfusion, and systemic/limb hypotension.
c. Prophylactic, if high enough index of suspicion or with prolonged ischemia or ligated major vein, especially in the face of a proximal arterial injury, repair and reperfusion to the limb.
d. Mandatory for high compartment pressure with possible viability.
e. Surgical fasciotomy.
i. Lower extremity: a four-compartment fasciotomy through two incisions, one lateral and one medial (with large fascial incisions, approximately 25-cm long in each compartment).
ii. Upper extremity.
(a) Volar incision: crossing curvilinear across the wrist in to the hand (thenar) and curvilinear across antecubital fossa into the upper arm.
(b) Dorsal: longitudinal.
(c) Mobile wad: longitudinal (may have already been decompressed with volar incision).
f. Skin left open.
g. May require a late skin graft to cover the resulting defect if unable to reapproximate over 5 to 7 days.

2. Ocular compartment syndrome.
a. Emergent lateral canthotomy: optic nerve/retinal ischemia can occur within *60 minutes* of unrelieved pressure; permanent loss of vision in *1.5 to 2 hours*.

F. Complications.

1. Extremity.
a. Rhabdomyolysis.
b. Ischemic neuropathy.
c. Myonecrosis and fibrosis.
d. Renal failure from myoglobinemia.
e. Reperfusion syndrome: resulting in further swelling, higher compartment pressures.
f. Limb loss.
g. Fasciotomy in fractured extremities.
i. Prolonged bony healing.
ii. Increased incidence of nonunion.

2. Ocular: loss of vision.

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117 Sepsis and Multiorgan Failure

Marie Mullen

"Hectic fever (sepsis) at its inception is difficult to recognize but easy to treat. Left untended, it becomes easy to recognize but difficult to treat."
– Niccolo Machiavelli (1498)

I. GENERAL PRINCIPLES

A. Definitions.

1. Systemic inflammatory response syndrome (SIRS).
   a. Clinical response to nonspecific injury, including trauma, burns, infection, pancreatitis, or alternative inflammatory insult.
   b. Clinical components of SIRS (two elements required to define).
      i. Temperature ≥38°C or ≤36°C.
      ii. Heart rate ≥90 per minute.
      iii. Respirations ≥20 per minute.
      iv. Leukocyte count >12,000 or <4,000 or >10% bands.
      v. $Paco_2$ < 32 mm Hg.
2. Sepsis.
   a. Documented or suspected infection and evidence of clinical inflammatory response.
   b. 1992 criteria—Two or more SIRS criteria with associated infection define sepsis.
   c. 2001 criteria—Documented or suspected infection with some markers of inflammation (Table 117-1).
3. Severe sepsis.
   a. Sepsis with associated organ dysfunction or tissue hypoperfusion (Table 117-2).
4. Septic shock.
   a. Sepsis with refractory hypotension after appropriate fluid resuscitation.
   b. Suggested appropriate resuscitation of at least 30 mL/kg crystalloid minimum to be considered refractory.
5. Multiple-organ dysfunction syndrome (MODS).

TABLE 117-1 Diagnostic Criteria Sepsis

Infection[a], documented or suspected, and some of the following:[b,c]

General variables
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min^{-1} or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 h)
- Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables
- Leukocytosis (WBC count >12,000 μL^{-1})
- Leucopenia (WBC count <4,000 μL^{-1})
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic variables
- Arterial hypotension[b] (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
- SvO_2 > 70%[b]
- Cardiac index >3.5 $L \cdot min^{-1} \cdot M^{-2}$[3]

Organ dysfunction variables
- Arterial hypoxemia (PaO_2/FIO < 300)
- Acute oliguria (urine output <0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ or 45 mmol/L for at least 2 h)
- Creatinine increase >0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or aPTT >60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000 μL^{-1})
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)

Tissue perfusion variables
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling

[a]Infection defined as a pathologic process induced by a microorganism.
[b]SvO_2 saturation >70% is normal in children (normally, 75%–80%), and CI 3.5–5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children.
[c]Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO_2, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.
Source: From Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250–1256.

TABLE 117-2 Elements Suggestive of Organ Failure

Sepsis-induced hypotension
Lactate greater than the upper limits of normal laboratory results
Urine output < 0.5 mL/kg/h for >2 h, despite adequate fluid resuscitation
ALI with PaO_2/FIO_2 <250 in the absence of pneumonia as infection source
ALI with PaO_2/FIO_2 <200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 mol/L)
Bilirubin > 2 mg/dL (34.2 mol/L)
Platelet count <100,000
Coagulopathy (INR > 1.5)

Dellinger RP, Levy M, Rhodes A et al., Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. 2012 *Crit Care Med* 2013;41(2):580–637.

a. Disease spectrum in which one or more organ systems are unable to maintain homeostasis without support in an acutely ill patient.
b. MODS has many potential sources. Sepsis is one of the most common (Table 117-3).

B. Epidemiology.

1. Severe sepsis represents 20% of all ICU admissions in the United States (US).
2. Severe sepsis is the number one cause of death in the non–coronary care ICU and the 10th leading cause of death in the US.
3. Severe sepsis has an estimated 28% to 50% mortality rate.
4. Septic shock has an estimated mortality of 60%.
5. MODS is a leading cause of death in the ICU. Depending on the number of organ systems involved, MODS can carry an 80% mortality rate.

II. PATHOPHISIOLOGY

A. Infection.

1. Sepsis is an overwhelming and complicated proinflammatory response to infection.
2. Inciting organisms have changed with time. Change is connected to drug resistance.
3. Gram-negative and gram-positive organisms are each separately linked to 25% of sepsis-related infections.
4. Mixed gram-negative and gram-positive infections account for about 15% of causative infections.
5. Fungi associated with 5% to 10% of infections.

B. Pathogen induction.

1. Inflammatory response starts with recognition of pathogen molecular components by receptors on cells of the innate immune system.

TABLE 117-3 Risk Factors for MODS

Infection
- Peritonitis and intra-abdominal infection
- Pneumonia
- Necrotizing soft tissue infections
- Tropical infections (e.g., *falciparum* malaria, typhoid fever, dengue fever)

Inflammation
- Pancreatitis

Ischemia
- Ruptured aortic aneurysm
- Hemorrhagic shock
- Mesenteric ischemia

Immune reactions
- Autoimmune disease
- Reactive hemophagocytic syndrome
- Antiphospholipid antibody syndrome
- Transplant rejection
- Graft versus host disease

Iatrogenic causes
- Delayed or missed injury
- Blood transfusion
- Injurious mechanical ventilation
- Treatment-associated increased intra-abdominal pressure

Intoxication
- Drug reactions (anticonvulsants, carboplatin, antiretrovirals, colchicines, propofol, amiodarone, monoclonal antibodies)
- Arsenic
- Drug intoxication (ecstasy, cocaine, salicylates, acetaminophen)

Endocrine
- Adrenal crisis
- Pheochromocytoma
- Thyroid storm
- Myxedema coma

Reproduced from Mizock BA. The multiple organ dysfunction syndrome. *Dis Mon* 2009;55:476–526.

2. Innate immune cell members consist of neutrophils, macrophages, monocytes, basophils, eosinophils, natural killer cells, mast cells, dendritic cells, and platelets.
3. Pathogen-inducing components capable of triggering an immune response are numerous and include lipopolysaccharide (LPS) from gram-negative bacteria; lipoteichoic acid from gram-positive bacteria, and flagellin.

C. Toll-like receptors (TLRs).

1. TLRs are cell membrane proteins that exist to specifically recognize a variety of pathogen- and tissue damage–associated components.

2. TLRs are a key element to initiating the immune response. TLRs along with other proteins comprise a cadre known as pattern recognition receptors (PRRs).
3. Activation of TLRs leads to initiation of the inflammatory cascade. This includes activation of the critical transcription factor NF-κB. Ongoing response is variable and host dependent.
4. Key TLRs include TLR-2 and TLR-4.

D. Mediators of sepsis.

1. Activation of the inflammatory cascade precipitates the release and interaction of myriad important mediators.
2. These mediators encompass cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor–α(TNF-α).
3. High mobility group box-1 (HMGB-1) is a unique cytokine that can provoke a lethal proinflammatory response.
4. Additional mediators include platelet-activating factor (PAF), bradykinin, nitric oxide, and elements of the complement system.

E. End-organ consequences.

1. Sepsis-associated mediators contribute to end-organ damage. Damage elements include vasodilatation and altered perfusion, microvascular permeability and thrombosis, myocardial depression, mitochondrial dysfunction, maladaptive use of cellular nutrients, and cellular apoptosis.

III. DIAGNOSIS

A. Clinical features of sepsis.

1. Early sepsis consists of suspected or confirmed infection and evidence of inflammation (Table 117-1). Early signs include SIRS criteria (tachycardia, tachypnea, etc.) and hyperglycemia.
2. Progression to severe sepsis leads to evidence of organ dysfunction, including oliguria, renal insufficiency, altered mental status, coagulopathy, and significantly elevated lactic acid levels.
3. Late sepsis deteriorates to present with fluid refractory hypotension (septic shock) and acute respiratory distress syndrome (ARDS). MODS will likely manifest in the late stages of sepsis as well.

B. Inflammatory source identification.

1. Early inflammatory source identification and treatment are critical actions. Missed source control prolongs the inflammatory response and attenuates resuscitation efforts.
2. Most common sources of infection include the respiratory tract and the urinary tract. Other potential sources can be found in Table 117-4.
3. Primary organisms involved are gram-positive or gram-negative organisms separately or in a mixed infection. Fungi or anaerobes account for 10% of sepsis-related infections.
4. Concerted effort to identify the cause is paramount. Evaluation should include blood and urine cultures. Cerebrospinal fluid (CSF), body fluid, and stool cultures should be considered as appropriate. Radiologic imaging needs to be initiated as indicated.

TABLE 117-4 Common Sites and Diseases Associated with Sepsis/SIRS

Organ system	Location	Disease
Respiratory	Upper respiratory tract	Sinusitis Mastoiditis
	Lower respiratory tract	Pneumonia Lung abscess Empyema
Gastrointestinal	Mediastinum	Esophageal rupture/perforation
	Hepatobiliary	Hepatic abscess Cholangitis Cholecystitis
	Intra-abdominal	Intestinal infarction/perforation pancreatitis Intra-abdominal/diverticular abscess
Cardiovascular	Mediastinum	Postoperative mediastinitis
	Native or prosthetic cardiac valve	Endocarditis
Genitourinary	Kidney, ureter, and bladder	Perinephric abscess Pyelonephritis Cystitis
Neurologic	Brain and meninges	Meningitis Intracranial abscess
Dermatologic	Traumatic wound, surgical wound, or burn site	Soft tissue abscess Necrotizing fasciitis Infected decubitus ulcer Full- and partial-thickness burn
Prosthetic	Central/peripheral venous catheter Arterial catheter Ventriculoperitoneal shunt Dialysis catheter	Catheter infection
	Articular prosthetic device Dialysis graft/shunt	Infected prosthesis
Other	Vascular system	Septic thrombophlebitis

C. Predisposition, Infection, Response, and Organ dysfunction (PIRO) sepsis-staging system.

1. Scoring system for sepsis that attempts to better describe prognosis and response to therapy. Based on the cancer TMN scale.
2. Stratifies patients based on four criteria (*PIRO*).
   a. **P**—Predisposition to develop and respond to sepsis. Includes age, comorbidities, and genetic factors that impact occurrence and progression of sepsis.

b. **I**—Infection elements. Evaluates infection site, severity, type, and organism susceptibility.
c. **R**—Response to infection. Measures host reaction to infection using clinical and laboratory values, including vital signs, white blood cell count, and lactate levels.
d. **O**—Organ dysfunction presence. Considers number of organ dysfunction markers.

3. PIRO is a relatively new and developing concept. Future use may enable individualization of prognosis and treatment.

IV. MODS

A. Background.

1. Up to 15% of all medical and surgical patients will develop MODS.
2. Often the consequence of initial successful resuscitation.
3. A more refined definition describes MODS as the manifestation of potentially reversible physiologic dysfunction in two or more organ systems not originally associated with the initial disease and developing as a consequence of a serious life-threatening insult.
4. Number of organs involved and duration of failure directly impact mortality.
5. Single-organ failure carries a 20% mortality rate; two-organ involvement invokes a 40% mortality rate; injury involving three organs predicts an 80% mortality estimate.
6. Sepsis patients tend to have a predominance of lung involvement (68%) followed by abdominal injury (22%).

B. Scoring systems.

1. MODS mortality is linked directly to severity of organ dysfunction.
2. Multiple scoring systems exist to stratify mortality and initial disease severity.
3. Scoring changes showing improvement or deterioration serve as useful quality indicators in the ICU.
4. Two frequently used scales include the sequential organ failure assessment (SOFA) and the multiple-organ dysfunction score (Table 117-5).

C. Pathophysiology.

1. MODS evolution is not completely understood. Research efforts have been made to better understand its method of action and injury.
2. One of the better understood pathologic mechanisms is the disordered immune response (Fig. 117-1).
   a. Innate immune system involving TLR is activated. This is followed by release of inflammatory cytokines (IL-1, IL-6, TNF-α).
   b. Inflammatory response potentiates and activates the complement and coagulation system. Cytokines prime neutrophils, leading to the release of superoxides and other mediators.
   c. In MODS, this immune response progresses unchecked. Organ damage ensues, including capillary leak, edema, microcoagulation, tissue hypoxia, and subsequent mitochondrial injury.

TABLE 117-5 Clinical Measurement Systems to Assess Organ Dysfunction

Parameter	SOFA	Score	MODS	Score
Respiratory	PaO_2/FiO_2 ventilation	0–4	PaO_2/FIO_2	0–4
Coagulation	Platelet number Cell number	0–4	Platelet number	0–4
Hepatic	Bilirubin	0–4	Bilirubin	0–4
Cardiac	Blood pressure Vasopressor use	0–4	Blood pressure Heart rate CVP	0–4
CNS	Glasgow coma scale	0–4	Glasgow coma scale	0–4
Renal	Creatinine urine output	0–4	Creatinine urine output	0–4
Aggregate score	Add worst daily score	0–24	Add worst daily score	0–24

SOFA, sepsis-related organ failure assessment; MODS, multiple-organ dysfunction score; CNS, central nervous system.

3. The intestine is thought to contribute to MODS (gut hypothesis).
   a. Intestinal injury creates increased permeability. Mucosal disruption creates a cytokine-generating entity that potentiates the immune response.
   b. Tissue injury decreases the protective effect of gut-associated lymphoid tissue (GALT). Lack of nutrition further attenuates GALT potency.
   c. Tissue damage triggers virulence genes in commensal gut flora and potentiates damage to the intestine.
4. Elements of MODS are thought to further develop through an immune priming mechanism (the "Two Hit" hypothesis).
   a. The initial severe injury occurs followed by a more minor insult (second hit). The second lesser injury then generates an exaggerated immune response.
5. There is currently no unifying mechanism to explain MODS. It remains a concert involving the inflammatory cascade, the coagulation system, and tissue hypoperfusion leading to clinical organ dysfunction (Fig. 117-2).

V. TREATMENT

A. Timing is everything.

1. Severe sepsis, septic shock, and MODS are time-dependent disease processes. They are as time dependent as an acute myocardial infarction or acute ischemic stroke.
2. MODS management overlaps many of the principles used to approach severe sepsis and septic shock. This includes early source control, early resuscitation, and appropriate organ support using the most up-to-date literature.

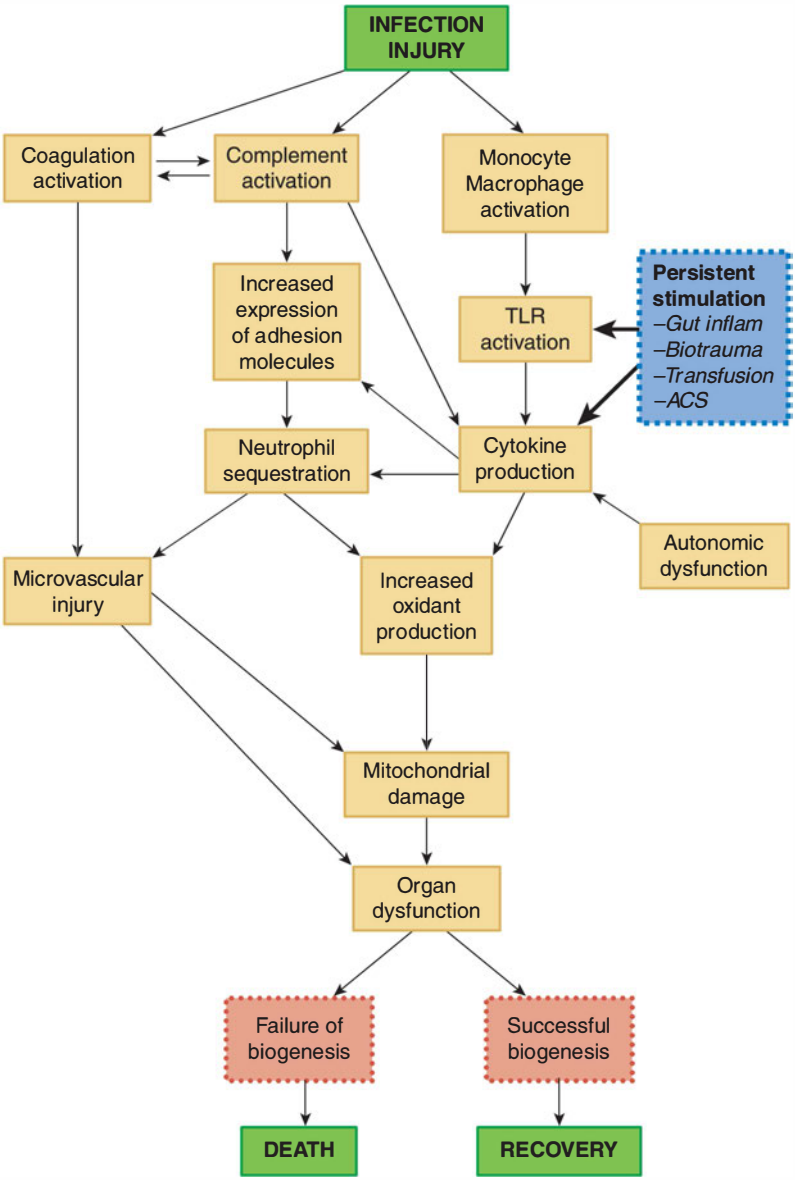

Figure 117-1. Overview of cellular and molecular mechanisms leading to MODS. TLR, Toll-like receptor; ACS, abdominal compartment syndrome. (Reused from Mizock BA. The multiple organ dysfunction syndrome. *Dis Mon* 2009;55:476–526.)

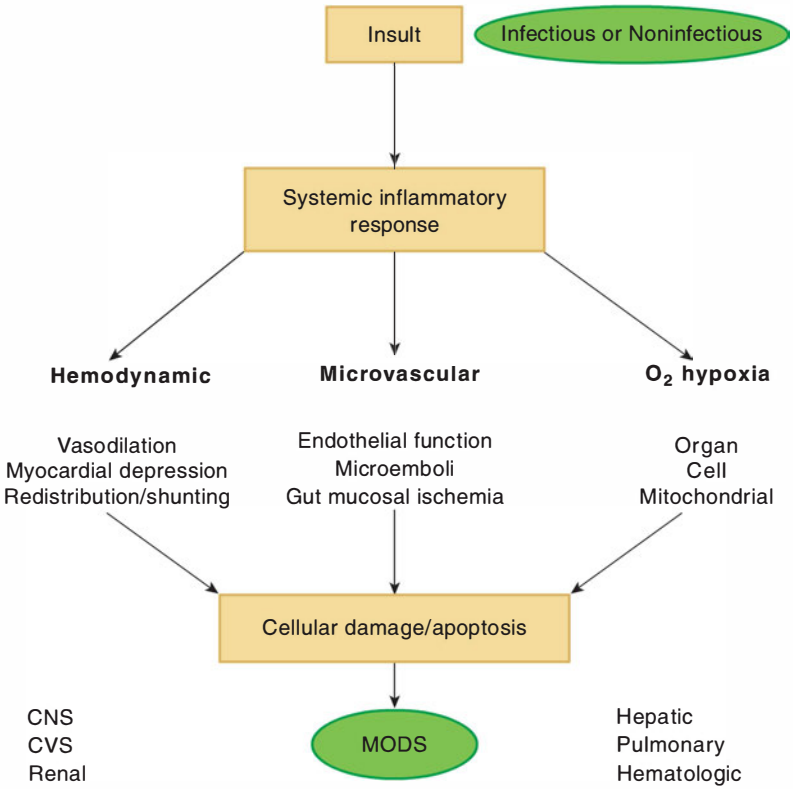

Figure 117-2. Multiple organ dysfunction syndrome (MODS) etiologic factors. CNS, central nervous system; CVS, cardiovascular system.

3. Initial severe sepsis treatment can be divided into care bundles. The Surviving Sepsis Campaign endorses a 3-hour and 6-hour bundle (Table 117-6). These bundles are then augmented with recommended supportive care measures.

B. Early goal-directed therapy (EGDT).

1. Patients with sepsis and a lactic acid level ≥ 4 mmol/L or sepsis and hypotension after initial fluid resuscitation merit EGDT.
2. Identification of global tissue hypoxia in the normotensive septic patient is crucial. An initial lactic acid level should be part of any labs ordered for a patient with suspected sepsis. If a patient is ill enough to require blood cultures, he is ill enough to order a lactic acid test.
3. EGDT requires placement of a central venous catheter (CVC) and the achievement of the following goals within 6 hours of resuscitation:
   a. Central venous pressure (CVP) 8 to 12 mm Hg (12 to 15 mm Hg for mechanical ventilation).
   b. Mean arterial pressure (MAP) ≥ 65 mm Hg.

TABLE 117-6 Surviving Sepsis Campaign Bundles

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad-spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dL)
   - Measure CVP[a]
   - Measure central venous oxygen saturation ($ScvO_2$)[a]
7) Remeasure lactate if initial lactate was elevated[a]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, $Scvo_2$ of 70%, and normalization of lactate.

c. Urine output ≥ 0.5 mL/kg/h.
d. Central venous oxygen saturation ($ScvO_2$) ≥ 70% or mixed venous (SvO_2) ≥ 65%.

4. Crystalloid resuscitation is the preferred and ongoing modality of fluid administration. Colloid, particularly albumin, may be added as an adjunct. Hetastarches and hydroxyethyl starches are not recommended for use. Recommended initial resuscitation is 30 mL/kg fluid as part of the 3-hour bundle.
5. CVP has limitations in volume assessment. Some authors recommend using such adjuncts as CVP variability, pulse pressure variation (PPV), stroke volume variation (SVV), passive leg raise (PLR), and ultrasound-guided vena cava variability to augment guided fluid resuscitation.
6. Vasopressor and inotrope use for refractory MAP and cardiac dysfunction.
   a. Norepinephrine is the preferred initial vasopressor agent in septic shock (0.05 to 1.5 μg/kg/min).
   b. Epinephrine recommended when an additional agent needed for hypotension (0.05 to 0.5 μg/kg/min). Epinephrine may be added or substituted in a refractory situation.
   c. Dopamine suggested in only selected low cardiac output or low heart rate states with low arrhythmia risk (5 to 20 μg/kg/min).
   d. May consider adding vasopressin 0.03 units/minute for refractory shock to augment MAP or decrease vasopressor requirement.
   e. Dobutamine is recommended for myocardial dysfunction in sepsis (2.5 to 20 μg/kg/min).
   f. Low-dose dopamine for renal protection has no clinical benefit and is not recommended.

g. Arterial catheter monitoring is recommended with vasopressor use.
h. Pulmonary artery catheter (PAC) use has not shown a benefit in comparison to the use of a CVC. Risks and complication of PAC insertion need to be considered prior to use.

7. Low $ScvO_2$ after fluid resuscitation may be addressed with several modalities. Consider transfusion for low $ScvO_2$ and a hematocrit (Hct) level <30, endotracheal intubation, and/or the use of dobutamine (2.5 to 20 μg/kg/min) to achieve $ScvO_2$ goals.
8. EGDT may be augmented by trending serial lactate levels toward normalization.

C. Early antibiotics and source control.

1. Equally important as EGDT.
2. Recommend broad empiric intravenous antibiotics based on presumed source within 1 hour of suspected diagnosis of severe sepsis and septic shock. (*High mortality if time window or organism missed.*)
3. At least one or more appropriate antibiotic agents recommended. Combination therapy considered for neutropenic patients or suspected *Pseudomonas* infections.
4. Antibiotic choice should involve evaluation of effectiveness against presumed source, local resistance patterns, tissue penetration, side effects, and potential medication interactions.
5. Consider fungal source when appropriate.
6. At least two peripheral blood cultures prior to antibiotic administration. (Do not delay antibiotics >45 minutes.)
7. Reassessment encouraged for de-escalation as soon as possible.
8. Frequent reevaluation considered for toxicity.
9. Source identification and control.
a. Cultures in addition to blood as appropriate—urine, CSF, body fluid, wound, stool.
b. Appropriate radiologic evaluations.
c. Emergency source control within 12 hours recommended. Measures may include abscess drainage, tissue debridement, or removal of indwelling devices.
d. Failure to appropriately cover an infecting organism or to obtain source control may create an ongoing infective insult that attenuates resuscitative measures.

D. Sepsis care adjuncts.

1. Corticosteroid use.
a. Critical illness–related corticosteroid insufficiency is a known phenomenon. Routine corticosteroid use is not recommended.
b. May consider low-dose hydrocortisone in cases of fluid- and vasopressor-refractory shock.
c. Consider 200 mg intravenous hydrocortisone per day if unable to restore hemodynamic stability with fluid resuscitation and vasopressors.

2. Glycemic control.
a. Hyperglycemia of critical illness is a recognized entity and linked to mortality.

   b. Protocolized insulin (other than tight glycemic control) and nutrient management recommended.
   c. Hypoglycemia may be missed with bedside glucose monitoring. Exercise caution in use of point-of-care glucose testing, as levels may be overestimated.
3. Lung-protective strategies.
   a. Sepsis accounts for a significant number of cases of acute lung injury (ALI) and ARDS.
   b. Low tidal volume mechanical ventilation is a key component to ALI/ARDS care.
   c. Recommend setting a goal tidal volume of 6 mL/kg ideal body weight for mechanically ventilated sepsis ALI/ARDS patients.
   d. Limit plateau pressure to ≤30 cm H_2O.
4. Prophylaxis.
   a. Deep venous thrombosis (DVT) prophylaxis should be administered to all patients unless contraindicated.
   b. Stress ulcer prophylaxis indicated for all patients unless contraindicated.
5. Renal replacement therapy should be initiated for MODS and kidney failure.
6. For MODS, some literature supports the use of antimicrobial agents to decontaminate the oropharynx and digestive tract to reduce the risk of ventilator pneumonia and eliminate harmful intestinal bacteria. These practices remain controversial in the US due to antimicrobial stewardship issues and concerns for higher levels of antibiotic resistance in the US.
7. Early enteral nutrition is supported in the management of MODS.
8. Comfort-only care.
   a. Communication with the patient and family is an important element of care. Early discussions regarding expected outcome should be initiated. Aggressive care needs to be balanced with patient wishes.

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SECTION 13

Neurologic Problems in the Intensive Care Unit

David A. Drachman and David Paydarfar

118 An Approach to Neurologic Problems in the Intensive Care Unit

David A. Drachman

I. GENERAL PRINCIPLES

A. Patients with neurologic problems present in the intensive care unit (ICU) as primary neurologic problems or as neurologic complications secondary to medical or surgical disorders. Only a few common neurologic *situations* occur in the ICU, although they can be caused by many *diseases.*

1. Depressed state of consciousness, coma.
2. Altered mental function.
3. Required support of respirations or other vital functions.
4. Monitoring: increased intracranial pressure (ICP), respirations, consciousness.
5. Determination of brain death.
6. Prevention of further damage to the central nervous system (CNS).
7. Management of seizures or status epilepticus.
8. Evaluation of a neurologic change occurring as a result of known medical disease.
9. Management of medical disease developing during neurologic illness.
10. Acquired weakness during an ICU stay.

B. Primary neurologic problems in the ICU include the following:

1. Stroke.
2. Guillain-Barré syndrome.
3. Status epilepticus.
4. Myasthenia gravis.
5. Head or spinal cord trauma.

C. Neurologic complications of medical disease are far more common than primary neurologic problems. They include:

1. Impaired consciousness following cardiac arrest and cardiopulmonary resuscitation.
2. Altered mental status from metabolic disorders.
3. Development of delirium.
4. Critical care neuromyopathy.
5. Focal neurologic deficits, or impaired consciousness, in a patient with multisystem disease.

D. Indications for neurologic consultation in the ICU.

1. *Depressed state of consciousness.* Depressed consciousness ranges from lethargy to coma and raises many questions:
   - **a.** Is there a focal brainstem lesion or diffuse cerebral involvement?
   - **b.** Is there an anatomic lesion or a metabolic disorder?
   - **c.** Have vital brainstem functions been impaired?
   - **d.** Is ICP increased?
2. The most common *primary neurologic causes* of depressed consciousness include:
   - **a.** Head trauma.
   - **b.** Intracranial hemorrhage.
   - **c.** Nonconvulsive seizures.
3. The *secondary conditions* seen most often are
   - **a.** Metabolic–anoxic disorders.
   - **b.** Drug intoxications.
   - **c.** Diabetic ketoacidosis.
4. It is crucial to establish whether depressed consciousness is the result of
   - **a.** Intrinsic brainstem damage.
   - **b.** Increased ICP.
   - **c.** Toxic substances.
   - **d.** Widespread anoxia/ischemia.
   - **e.** Other, less common causes.

II. DIAGNOSIS

A. In the patient with depressed consciousness, it is particularly important to identify *as rapidly as possible* the component(s) that may be treatable!

1. **Neurologic examination of patients with stupor or coma.** Examination of the patient with depressed consciousness includes evaluation of (a) mental status, (b) cranial nerve functions, (c) motor functions and coordination, (d) reflexes, (e) sensation, and (f) vascular integrity; supplemented by appropriate laboratory studies.

a. *Mental status.*
  i. Detailed evaluation of memory and cognitive function is rarely possible in lethargic patients and is impossible when stupor or coma is present.
  ii. Estimate the responsiveness of the patient, including vital functions, respiratory pattern, eye opening, response to painful stimuli, and speech.

b. *Cranial nerve evaluations*: Vision (e.g., blink to threat), pupils (size and response), corneal reflexes, "doll's eyes" responses, and, if absent, ice water caloric response, cough, facial movements to pain, and gag reflex are tested.

c. *Motor function*: Evaluate by observing all limbs for spontaneous movement, symmetry, and adventitious movements. Pinch or other noxious stimulus may help evaluate purposeful defensive movements.
  i. Decerebrate (four-limb extensor) or decorticate (upper limbs flexor, lower limbs extensor) rigidity is observed.
  ii. Tone is assessed for spasticity or rigidity.

d. *Reflexes*: Deep tendon reflexes, grasp, suck, snout, and plantar reflexes are evaluated.

e. *Sensation*: Pain is often the only testable sensation; withdrawal from pinprick in the feet must be distinguished from an extensor plantar response.

f. *Vascular status*: Listen for bruits over the carotid, subclavian, and vertebral arteries.

2. Laboratory studies.

a. Imaging studies: Magnetic resonance imaging (MRI) or computed tomography (CT) can reveal evidence of stroke, hemorrhage, trauma, tumor, and so forth, despite the difficulty of obtaining these studies.

b. Electroencephalography (EEG): This reveals seizure activity, functional state, symmetry, certain toxic–metabolic conditions. Can be performed at the bedside.

c. Metabolic studies: Electrolytes, ammonia, pH, O_2 saturation, renal function, hepatic function, toxic substances, and others.

3. Interpretation. This examination reveals the patient's state of consciousness, the integrity of brainstem reflexes, the presence of focal versus diffuse neurologic deficits, and provides information on specific metabolic disorders.

B. Management of patients with depressed consciousness depends on determining the cause and applying the appropriate techniques for eliminating toxins, reducing ICP, and maintaining vital functions.

1. Altered mental function: In the awake patient, disorders that affect mental function can produce patterns of confusion, delirium, aphasia, dementia, or isolated memory impairment. Ask the following questions:

a. Is the abnormal mentation a recent change or long-standing?

b. Did the change develop abruptly after surgery, cardiac arrest, or other event?

c. Is the mental change improving, worsening, or stable?

2. Confusion and delirium: often result from *metabolic* or *toxic* disorders; they are commonly reversible.
3. Persistent aphasia and *isolated* memory impairment: suggest focal anatomic damage to the brain. Neurologic examination for localization and imaging studies are useful.
4. Dementia/cognitive impairment: can be assessed *only* in patients with a clear sensorium; it cannot be evaluated in patients with depressed consciousness, confusion, or delirium. Cognitive impairment can indicate either *reversible* (drug-induced, depression-related) conditions or *irreversible* damage (diffuse anoxia, ischemia, strokes, or a degenerative dementia).
5. **Recent change of mental status in the ICU requires evaluation by an experienced neurologist as early as possible!**

C. Support of respiration and other vital functions.

1. Respiratory support is needed for neurologic patients with
   a. Loss of brainstem control of respiration.
   b. Impairment of effective transmission of neural impulses to respiratory muscles.
   c. Brainstem lesions produce characteristic respiratory patterns, depending on the site of damage (e.g., central neurogenic hyperventilation, Cheyne-Stokes or periodic breathing, apnea). Transmission of respiratory impulses can be impaired at the cervical spinal cord, anterior horn cells, peripheral nerves, neuromuscular junctions, or muscles of respiration. Traumatic cervical cord injuries, amyotrophic lateral sclerosis, the Guillain-Barré syndrome, myasthenia gravis, and muscular dystrophy interfere with breathing at these different levels. Some conditions are transitory (Guillain-Barré syndrome) or treatable (myasthenia gravis), with *complete recovery* if respiration is successfully maintained.

D. Monitoring ICP and state of consciousness. Head trauma, subarachnoid hemorrhage, tumor, and stroke may require neural monitoring.

1. Lethargic patients should be observed for increased ICP caused by cerebral edema, intracranial (subdural, epidural, intracerebral) hemorrhage, or both.
2. Once uncal or tonsillar *herniation* with brainstem compression occurs, the secondary brain injury may far outweigh the initial damage (methods for monitoring ICP and assessing consciousness with the Glasgow coma scale are described in Chapter 15 and the Appendix of this manual).

E. Determination of brain death.

1. Death of the brain and brainstem is equivalent to death of the patient.
   a. Brain death is specifically a determination that the brain *and* the brainstem are already dead—*not* a *prediction* of unlikely useful recovery.
   b. The mnemonic *CADRE* is useful to remember the criteria for brain death: **c**oma, **a**pnea, **d**ilated fixed pupils, **r**eflex (brainstem) absence, and **E**EG silence.

F. Preventing further damage to the CNS.

1. In stroke, thrombolytic treatment or mechanical clot removal can reverse the ischemic process, and neuroprotective agents may prevent further damage.
2. Spinal cord compression by tumor requires decompression and/or radiation therapy to avoid cord transection.
3. *Cerebral ischemia, anoxia, hemorrhage, increased ICP, spinal cord compression, and other acute neurologic disorders require prompt institution of treatment.*

G. Managing status epilepticus. Status epilepticus threatens lasting deficits or death if not controlled.

1. Patients with *continuous* or *recurrent* seizures that cannot be promptly arrested must be treated in the ICU.
2. Therapy ranging up to general anesthesia and support including mechanical ventilation may be required.

H. Evaluating secondary neurologic disease in severe medical illness. Patients in the ICU with myocardial infarctions, subacute bacterial endocarditis, cardiac arrhythmias, pneumonia, renal disease, and other diseases that impact neurologic function may develop neurologic changes during treatment for the medical problem. These neurologic findings may result from the underlying disease or be coincidental; a neurologist should evaluate such patients.

I. Managing secondary severe medical disease in neurologic illness. Patients with chronic neurologic disorders often develop unrelated medical illness: for example, myocardial infarction that occurs in a demented patient or septicemia in a patient with multiple sclerosis. Early recognition of a change in the neurologic patient's condition is often critical to a successful outcome.

III. PROGNOSTIC AND ETHICAL CONSIDERATIONS

A. When severe damage involves the brain, physicians and their families often seek guidance regarding the probable outcome. Three critical questions should be addressed:

1. Will the patient survive?
2. Has irreversible brain damage occurred?
3. What is the likely degree of residual disability?

B. The most important consideration is whether *irreversible damage* has affected crucial brain areas, rather than the level of consciousness. The probability of neurologic recovery declines with age, size, and location of the lesion and duration of the deficit. Discontinuing sedation is critical in evaluating the patient's functional state. When prognosis is unclear, waiting and watching for an extra day is often of value. (Some reported statistical guidelines are of value in estimating recovery; see, e.g., Levy D, Caronna J, Singer B, et al. in Suggested Readings.).

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119 Altered Consciousness

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I. OVERVIEW

A. Introduction. Many diseases lead to acute impairment of consciousness, including some that are potentially life threatening but treatable if recognized early, and require a systematic and complete evaluation:

1. Rapid determination of the type of mental status change.
2. Administration of emergent treatment and life support measures when needed.
3. Obtaining a detailed history, physical and neurologic examinations, and ancillary studies.
4. Initiation of definitive treatment based on this assessment.

B. Pathophysiology.

1. Altered sensorium (state of consciousness) results from damage or dysfunction of the reticular activating system (RAS) in the brainstem and diencephalon, and/or their projections to *both* cerebral hemispheres.
2. Many structural/physiologic disorders can affect the RAS *or* both hemispheres diffusely and impair consciousness (Table 119-1).

C. Prognosis. Depends on the cause of coma and any secondary complications.

D. Diagnosis. The clinician must distinguish among potential causes, including normal sleep, coma, status epilepticus, akinetic mutism, locked-in state, and aphasia.

E. Treatment. Depends on the underlying cause and the presence or absence of cerebral edema.

II. THE PATIENT WHO APPEARS UNCONSCIOUS

A. General principles. Some patients appear to be unconscious when this is not the case. The differential diagnosis includes the following:

1. Normal sleep (can be aroused to complete wakefulness by verbal or physical stimulation).
2. Psychogenic coma (demonstrate clinical and electroencephalographic [EEG] evidence of wakefulness).
3. Locked-in state (awake and can communicate by vertical eye movements).
4. Nonconvulsive status epilepticus (impaired consciousness with EEG evidence of continuous seizures).
5. Stupor/coma (sustained arousal by stimuli cannot be obtained).
6. Brain death (absence of brain activity clinically and by ancillary testing).

TABLE 119-1 Differential Diagnosis of Impaired or Altered Consciousness

I. Impaired consciousness with focal or lateralizing signs of brain disease:
- A. Neoplastic or inflammatory mass lesions: brain tumor, brain abscess
- B. Vascular disease: cerebral hemorrhage, thrombosis, embolism
- C. Traumatic brain injury: contusion, subdural, or epidural hematoma

II. Impaired consciousness with signs of meningeal irritation:
- A. Septic[a]: infectious meningitis (bacterial, mycobacterial, viral, fungal, parasitic)
- B. Vascular: subarachnoid hemorrhage
- C. Neoplastic: leptomeningeal carcinomatosis or lymphoma
- D. Rheumatologic conditions: meningeal granulomatous disorders (e.g., sarcoid, polyangiitis granulomatosis previously referred to as Wegener granulomatosis)

III. Impaired consciousness without focal, lateralizing, or meningeal signs:
- A. Toxic encephalopathy: alcohol, barbiturate, opiates, carbon monoxide poisoning, serotonin syndrome, neuroleptic malignant syndrome, tricyclic antidepressants, amphetamines, anticholinergic agents, sedatives, carbon monoxide, and heavy metal toxins
- B. Metabolic[b]: anoxia/hypoxemia, hypercapnia, hyponatremia, hypoglycemia, hyperglycemia, uremia, hepatic failure, hyperthermia, hypothermia, hypercalcemia, thiamine, or cobalamin deficiency
- C. Septic: infectious encephalitis, bacterial and viral encephalitis, septicemia, pneumonia, rheumatic fever, and connective tissue diseases
- D. Vascular: hypertensive encephalopathy
- E. Acute hydrocephalus: obstructive
- F. Traumatic: concussion, diffuse axonal injury
- G. Electrical: nonconvulsive status epilepticus, seizures
- H. Situational psychoses: intensive care unit, puerperal, postoperative, or posttraumatic psychoses; severe sleep deprivation can be complicating factor
- I. Neoplastic/inflammatory: paraneoplastic syndromes, vasculitis, and lupus cerebritis

[a]Meningismus is often absent in deeply comatose patients with meningeal inflammation.
[b]Metabolic derangements can produce focal signs, for example, ocular motility disturbance due to thiamine deficiency and focal deficits with hypoglycemia.
Adapted from Adams RD, Victor M. *Principles of neurology*. 4th ed. New York: McGraw-Hill, 1989.

B. Prognosis.

1. Depressed consciousness: Prognosis depends on the underlying cause, degree of reversibility, and presence of secondary brain damage from effects of raised intracranial pressure (ICP) or tissue shifts.
2. Locked-in state: Patients usually have permanent paralysis but can communicate through blinks. Acute locked-in state can sometimes be reversible with treatment of the underlying cause (i.e., thrombolytic therapy for a basilar artery stroke).

3. Status epilepticus: Usually reversible with antiepileptic drugs but may sustain permanent damage after prolonged seizure activity. When seen in anoxic coma, indicates a poor prognosis for recovery.
4. Stupor/coma: Prognosis depends on anatomic damage, physiologic, or biochemical etiology.

C. Diagnosis.

1. Rapid evaluation for the presence of neck rigidity on flexion (meningitis or subarachnoid hemorrhage), needle marks (drug overdose), hypoglycemia, or asymmetric dilated pupils (impending herniation) should be a priority before a more detailed examination.
2. Detailed history of onset, preceding events, past medical history, and the medication/drug history is crucial to establishing the correct diagnosis.
3. In mild brain dysfunction (drowsiness, hypersomnolence), mild sensory stimulation results in orientation and appropriate responses are made. In more severe brain dysfunction (stupor), more severe and sustained sensory stimuli are required to achieve transient arousal. Patients may have purposeful movements when aroused but lack normal content of consciousness.
4. Apparently comatose patients demonstrating active resistance, rapid closure of the eyelids, pupillary constriction to visual threat, fast phase of nystagmus on oculovestibular or optokinetic testing, and avoidance of self-injury may have psychogenic coma.
5. If spontaneous blinking is present in a paralyzed patient, appropriate responses may be elicited to questions, indicating normal cortical function (locked-in syndrome).
6. Severe brain dysfunction results in coma, from which patients cannot be aroused.
7. Nonfocal neurologic examination is suggestive of a toxic–metabolic coma, with some exceptions (meningoencephalitis, subarachnoid hemorrhage, bilateral subdural hematomas, or thrombosis of the superior sagittal sinus) (Table 119-1).
8. Presence of focal neurologic signs (cranial nerves or motor system) suggests a *structural lesion* as the underlying cause of coma.
9. Brain death is the irreversible destruction of the brain (total absence of all cortical and brainstem function), although spinal cord reflexes may remain.
   a. Pupils are in midposition, are round, and do not respond to light.
   b. The Apnea test. No inspiratory effort (i.e., central apnea) even when arterial carbon dioxide tension (PCO_2) is raised to levels that should stimulate respiration. Sedating medications, drug intoxications, metabolic disturbances, hypothermia, and shock should be excluded as complicating conditions in determining brain death.

D. Ancillary tests.

1. Imaging.
   a. Computed tomographic (CT) or magnetic resonance imaging (MRI) scan without contrast demonstrate intracranial hemorrhage and hydrocephalus.
   b. Contrast enhancement is indicated for the detection of infections or neoplastic masses.

c. MRI demonstrates ischemia within minutes after stroke onset.
d. CT and MR angiography or conventional angiography may be indicated if vascular causes are suspected.

2. Comprehensive metabolic profile, blood gases, and toxic screen must be performed, especially if CT and MRI fail to demonstrate a structural lesion.
3. The cerebrospinal fluid must be examined if meningoencephalitis or subarachnoid hemorrhage is suspected.
4. EEG is most useful in suspected seizures, as a confirmatory test for brain death, in suspected infections (herpes encephalitis, Creutzfeldt-Jakob disease), and to demonstrate normal rhythm and reactivity in locked-in syndrome and psychogenic coma.

E. Treatment.

1. Definitive treatment of altered consciousness depends on the underlying cause.
2. Reversal of depressed consciousness with intravenous thiamine, glucose, or naloxone often provides rapid diagnostic clues about unsuspected thiamine deficiency, hypoglycemia, or opioid overdose, respectively.
3. In cases of suspected clinical herniation, emergent administration of osmotherapy with mannitol or hypertonic saline, and emergent neurosurgical consultation, may be needed.
4. In suspected cases of acute cerebral ischemia, emergent stroke neurologic evaluation is indicated for consideration of tPA, clot retrieval, or a neurointerventional procedure.
5. Fluid replacement, oxygenation, suctioning, positioning, nutrition, corneal protection, and bowel and bladder care are essential.
   NB: Sedating drugs confound the accurate diagnosis and monitoring of the patient's neurologic condition and *should be avoided or minimized whenever possible.*
6. In patients with ischemia/hypoxia in the setting of cardiac arrest–induced hypothermia, may limit neurologic damage and improve outcome (see Chapter 24).

III. THE PATIENT APPEARS AWAKE BUT IS CONFUSED OR NONCOMMUNICATIVE

A. General principles. Patients with this clinical presentation may have acute confusional state, delirium, nonconvulsive seizures, receptive aphasia, or akinetic mutism.

1. Acute confusional state: Easily distracted, poor attention span with resultant poor recall, and short-term memory.
2. Delirium (see chapter 142 that deals with this in the Psychiatry section).
   a. Behavior that suggests an acute confusional state.
   b. Hypervigilance with delusions and often visual hallucinations.
   c. Autonomic hyperactivity.
   d. Psychomotor retardation in "quiet delirium."

3. Nonconvulsive status epilepticus. Signs that are suggestive of this diagnosis are episodic staring, eye deviation or nystagmoid jerks, facial or hand myoclonic activity, or automatisms.
4. Receptive aphasia.
   a. Unable to respond to or repeat commands.
   b. Fluent but jargon speech with paraphasias (word substitution).
5. Akinetic mutism.
   a. Brainstem function is intact, and sleep–wake cycles may be present.
   b. Little evidence is seen of cognitive function. Patient may open eyes to auditory stimulation or track moving objects, but only a paucity of spontaneous movement occurs.
6. Persistent vegetative state.
   a. Similar to akinetic mutism, more severe and usually follows prolonged coma.
   b. Complex subcortical responses are absent, but decorticate or decerebrate posturing and rudimentary subcortical responses (e.g., yawn, cough) are seen.
7. Minimally conscious state.
   a. Similar to persistent vegetative state but shows some evidence of self and environmental awareness, visual tracking, follows simple commands, gives gestural yes or no responses, purposeful behaviors.
   b. Transitional phase of recovery from coma or after vegetative state.

B. Diagnosis.

1. The history is critical in determining the cause of the patient's condition, and efforts to locate family members, witnesses, and medication lists are almost always fruitful.
   a. Knowledge of preexisting cerebral dysfunction (e.g., dementia, multiple sclerosis, mental retardation) is important in determining the degree of depressed consciousness or confusion expected for a specific systemic derangement (e.g., hyponatremia, sepsis, drug intoxication).
   b. A reliable account of the tempo of loss of consciousness is important. For example, rapid-onset coma in a healthy person suggests intracranial hemorrhage, brainstem ischemic stroke, meningoencephalitis, an unwitnessed seizure, or drug intoxication.
2. Focal neurologic signs suggest a structural cause of altered consciousness, although focal weakness or partial motor seizures sometimes occur in metabolic encephalopathies (e.g., hypoglycemia). Other falsely localizing signs include sixth nerve palsies caused by transmitted increased ICP, and visual field cuts caused by compression of the posterior cerebral artery. Conversely, a nonfocal examination does not invariably indicate toxic–metabolic encephalopathy, although it often will cause symmetric neurologic dysfunction (Table 119-2).
3. Treatment. Refer above to treatment of impaired consciousness.

TABLE 119-2 Classification of Causes of Altered Consciousness Based on Most Common Clinical Presentation

1. Depressed consciousness or acute confusional state *without* focal or lateralizing neurologic signs and without signs of meningeal irritation.[a]
   - Metabolic disorders: hepatic failure, uremia, hypercapnia, hypoxia, hypoglycemia, diabetic hyperosmolar state, hypercalcemia, thiamine or cobalamin deficiency, hypotension
   - Drug intoxications or poisoning: opiates, alcohol, barbiturates, tricyclic antidepressants, amphetamines, anticholinergic agents, other sedatives, carbon monoxide, heavy metal toxins
   - Infectious and other febrile illnesses: septicemia, pneumonia, rheumatic fever, connective tissue diseases
   - Nonconvulsive status epilepticus or postconvulsive lethargy
   - Situational psychoses: intensive care unit, puerperal, postoperative, or posttraumatic psychoses; severe sleep deprivation can be complicating factor
   - Abstinence states (i.e., withdrawal states): alcohol (delirium tremens), barbiturates, benzodiazepines
   - Space-occupying lesions: bilateral subdural hematoma, midline cerebral tumors (e.g., lymphoma, glioma), abscess
   - Hydrocephalus
2. Altered consciousness *with* signs of meningeal irritation
   - Infectious disorders: meningoencephalitis (bacterial, viral, fungal, parasitic)
   - Subarachnoid hemorrhage: brain contusion, ruptured aneurysm, or other vascular malformation
   - Rheumatologic conditions: meningeal granulomatous disorders (e.g., sarcoid, Wegener granulomatosis)
3. Altered consciousness with *focal or lateralizing neurologic signs*[b]
   - Space-occupying lesion: neoplasm, hemorrhage, inflammatory process (e.g., abscess, autoimmune encephalitis)
   - Cerebral ischemia or infarction: stroke, hypertensive encephalopathy

[a]Meningismus is often absent in deeply comatose patients with meningeal inflammation.
[b]Metabolic derangements can produce focal signs, for example, ocular motility disturbance due to thiamine deficiency and focal deficits with hypoglycemia.

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120 Metabolic Encephalopathy

Paula D. Ravin

I. BACKGROUND

A. Metabolic encephalopathy is defined as global brain dysfunction caused by a biochemical derangement.

B. There is often a fluctuating level of consciousness with nonfocal signs. Patients can present with the following:

1. Delirium (confusion, inattentiveness, sleeplessness, hallucinosis).
2. Depressed level of consciousness (drowsiness, stupor, coma).
3. Seizures, behavioral disturbances, visual impairment.

C. Metabolic encephalopathy is common in illnesses that cause multiorgan failure (see Table 120-1 for typical patient profiles).

D. The following increase the risk of developing metabolic encephalopathy:

1. Age older than 60 years.
2. Systemic infection.
3. Temperature dysregulation.
4. Chronic disease of the central nervous system (CNS).
5. Organ failure.
6. Endocrine disorders.
7. Multiple CNS-acting drugs.
8. Nutritional deficiency.
9. Alcoholism.
10. History of perinatal injury.
11. Sleep deprivation, sensory deprivation.

E. In cases of a correctible metabolic disorder, prompt treatment may result in reversal of encephalopathy.

F. Progression to stupor or coma may lead to prolonged encephalopathy and complications, with a poor neurologic outcome.

II. ETIOLOGY

A. Drugs and toxins (50%).

B. Hepatic, renal, or pulmonary failure (12%).

C. Endocrine or electrolyte disturbances (8%).

D. Other causes: thiamine deficiency (exacerbated by glucose loading), prolonged hypoglycemia, hypoperfusion during cardiac bypass, hyperthermia (>105°F), hyperammonemia, and severe hypertension.

TABLE 120-1 Patient Profile in Metabolic Encephalopathy

- Gradual onset over hours
- Progressive if untreated
- Waxing and waning level of consciousness
- Patient treated with multiple CNS-acting drugs
- Patient with organ failure, postoperative state, electrolyte or endocrine imbalance
- No evidence of CVA, brain tumor: nonfocal examination
- Can be heralded by focal or generalized seizures
- Increased spontaneous motor activity

CNS, central nervous system; CVA, cerebrovascular accident.

III. PATHOGENESIS

A. Altered substrate (glucose/oxygen) for neurotransmitter function.
B. CNS-depressant drug accumulation due to abnormal volume of distribution (decreased protein, high lipophilicity).
C. Impaired cerebral blood flow.
D. Abnormal cerebrospinal fluid (CSF) dynamics.
E. Altered neuronal function due to temperature and/or ionic changes.

IV. DIAGNOSIS.

Metabolic encephalopathy should be considered when a patient exhibits altered cognition or alertness. The clinical examination should include the following:

A. General physical examination.

1. Vital signs, breathing pattern, and pulse oximetry.
2. Funduscopy, to evaluate for papilledema (increased intracranial pressure), septic emboli.
   a. Cardiovascular examination: Global cerebral hypoperfusion may result from congestive heart failure.
3. Bowel sounds: Obstruction/perforation may cause agitation and changes in mental status.
4. Bladder distention: Retention can lead to agitation.

B. Neurologic examination.

1. Behavioral changes: inattention, diminished speech, disorientation, impaired short-term memory, indifference, blunted affect, waxing and waning consciousness, and visual hallucinations.
2. Abnormal extraocular eye movements should raise suspicion of brainstem stroke or thiamine deficiency; pupils are usually small and reactive, although they may be dilated in some toxic encephalopathies related to adrenergic excess (e.g., thyroid storm, cocaine overdose).
3. Respiratory pattern can be deranged in a variety of ways, including hyperventilation (e.g., acidosis), Cheyne-Stokes respiration,

hypoventilation, gasping, apneic episodes (central or obstructive), and hiccoughing.

4. Abnormal motor activity: tremors, myoclonus, asterixis, restlessness, chorea, muscle spasms, rigidity, and rigors.
5. Hyperreflexia and Babinski signs may be present.
6. Dysautonomia with widely fluctuating blood pressure and core temperature should raise suspicion of sepsis.

C. Metabolic encephalopathy should be distinguished from the following:

1. Brainstem stroke (see Chapter 123).
2. Increased intracranial pressure from an expanding mass lesion in the brain.
3. Meningoencephalitis (e.g., herpes).
4. Occult head trauma.
5. Nonconvulsive status epilepticus.

D. Metabolic encephalopathy due to thiamine deficiency (Wernicke-Korsakoff syndrome) should be suspected in all encephalopathic patients who are malnourished and/or have a history of alcohol abuse. Patients with the syndrome can present with oculomotor paresis, nystagmus, or pupillary abnormalities. Administration of glucose without parenteral thiamine can lead to an acute exacerbation of encephalopathy with permanent CNS injury.

E. PRES (Posterior Reversible Encephalopathy Syndrome) may occur in patients with abrupt hypertension, renal impairment, autoimmune disorders, transplantation, and treatment with immunosuppressive drugs. It is characterized by blindness, headache, confusion, seizures, and altered consciousness. The magnetic resonance imaging (MRI) shows characteristic white matter hyperintensities, typically (but not always) in the posterior parietal and occipital regions. It is a reversible syndrome; and removal of the trigger factors—chemotherapy, hypertension control, and treatment of other systemic disease—often results in recovery within a week, with slower resolution of the MRI changes.

V. LABORATORY STUDIES

A. Body fluids.

1. Toxicology screen, especially in patients with history of major depression, substance abuse. Include salicylates, barbiturates, opioids, amphetamines, alcohol, benzodiazepines, caffeine, and theophyllines.
2. Drug levels: digoxin, anticonvulsants, lithium.
3. Metabolic panel: blood urea nitrogen (BUN), creatinine, electrolytes, complete blood count (CBC), platelet count, thyroid-stimulating hormone (TSH), calcium, phosphate, arterial ammonia, blood gases, serum and urine osmolality, and blood glucose.
4. When indicated, CSF analysis for infection, inflammation, subarachnoid blood.
5. Urinalysis, urine culture, and blood cultures.

B. Electroencephalogram (EEG): Background slow wave activity or frontal triphasic waves are seen in metabolic encephalopathy. Epileptiform activity raises possibility of nonconvulsive status epilepticus.

C. Imaging studies.
   1. Computed tomography (CT) or preferably MRI scan of the brain, to evaluate for an acute structural lesion.
   2. Chest radiographic films, to evaluate for occult pneumonia.
   3. Abdominal radiographic films, to evaluate for bowel obstruction.

VI. TREATMENT

A. Correction of the underlying metabolic disturbance. Acute encephalopathy due to thiamine deficiency is a medical emergency. If suspected, give thiamine 100 mg intravenously daily for at least 3 days; the oral route is not as effective for rapidly repleting thiamine.

B. Improvement in cognition and arousal may lag behind the improvement in metabolic parameters by days to weeks in some cases.
   1. With underlying neurodegenerative disease, patients may not recover to their baseline level despite stabilized metabolic values.
   2. Avoid adding CNS-acting drugs such as stimulants and sedatives (especially benzodiazepines) that can worsen the behavioral changes of metabolic encephalopathy, and focus on addressing the inherent causes. Treatment with an antipsychotic such as haloperidol, Zyprexa, or Seroquel can be helpful for the management of agitated delirium.

VII. CONCLUSIONS

A. Metabolic encephalopathy is a common cause of altered neurologic function in the intensive care unit (ICU) setting.

B. It should be suspected when there is a fluctuating or impaired mental status, bouts of restlessness, and a nonfocal examination.

C. The causes are varied, but vigilant correction of metabolic disorders, reduction in CNS-acting drugs, and general supportive measures improve the outcome in most patients.

D. Patients in the ICU commonly have poor nutritional status and global encephalopathy. These patients should be treated empirically for acute thiamine deficiency.

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121 Generalized Anoxia/Ischemia of the Nervous System

Shashidhara Nanjundaswamy, Nils Henninger, Richard P. Goddeau Jr, and Majaz Moonis

I. GENERAL PRINCIPLES

A. Failure of blood flow (cardiac arrest) or reduced oxygenation to the brain (respiratory failure, carbon monoxide, or cyanide poisoning) for 4 to 5 minutes' duration results in brain damage.

B. Anoxia resulting from isolated respiratory arrest is better tolerated than when the primary event is a cardiac arrest.

II. PROGNOSIS.

Many factors determine the prognosis after anoxic brain insult. These include the cause of the anoxic/ischemic insult, effective time to reestablish circulation (arrest time [AT], cardiopulmonary resuscitation [CPR] time), level of consciousness, age of patient, and neurologic signs present at 24 to 72 hours.

A. Favorable prognostic indicators include the following:

1. Retained consciousness during the anoxic/ischemic insult.
2. Primary respiratory failure carries a better prognosis than primary cardiac arrest.
3. Recovery of multiple brainstem responses within 48 hours of arrest (pupillary, corneal, and oculovestibular).
4. Return of purposeful motor movements within 24 hours (localization of pain).
5. Younger age (children may do well even beyond this time period).
6. Hypothermia (e.g., cold water drowning).

B. Poor prognostic indicators in patients with persistent coma after 72 hours include the following:

1. The absence of pupillary responses at 24 hours or loss of pupillary reflexes at 72 hours.
2. No motor response or extensor-only response to pain at 72 hours.
3. Presence of diffuse cerebral edema on computed tomography (CT) scan with loss of gray–white differentiation.
4. Certain abnormal electroencephalogram (EEG) patterns, including burst suppression, α-coma, and low-voltage unreactive delta activity. Myoclonic status epilepticus has a very poor prognosis even with treatment.

5. Absence of bilateral N20 somatosensory response within 1 to 3 days after CPR.
6. Elevated levels of serum neuron specific enolase >33 μg/L at days one to three days post-CPR.

III. ETIOLOGY

A. Cardiac arrest from any cause.
B. Respiratory failure from any cause.
C. Poisoning (carbon monoxide, cyanide, others).

IV. PATHOPHYSIOLOGY.

Following these injuries, excess glutamate release results in activation of the excitotoxic cascade, calcium influx into neurons, and cell death.

V. DIAGNOSIS

A. History.
   1. Cardiac arrest.
   2. Respiratory failure.
   3. Drowning.
   4. Toxic drug exposure/intoxication.

B. Examination: Patients are comatose usually without focal neurologic deficits. Rarely soft neurologic signs have been documented.
C. Imaging and laboratory studies.
   1. CT or MRI scans to rule out structural lesions and brain herniation and demonstrate evidence of ischemic encephalopathy (cortical ribbon on diffusion MRI and loss of gray–white differentiation on CT).
   2. Blood glucose and liver function tests, including ammonia, blood urea nitrogen, and creatinine, should be obtained to rule out metabolic encephalopathy. Toxicologic screen should be obtained when the cause of coma is unknown. An immediate EEG if nonconvulsive status epilepticus is suspected.

VI. TREATMENT

A. Adequate oxygenation (Pao_2 at or over 100 mm Hg) and mean arterial blood pressure (90 to 110 mm Hg) should be maintained.
B. Head of the bed should be elevated to 30 degrees.
C. Underlying causes such as toxins or drug ingestion should be treated.
D. Cardiac arrhythmias should be controlled.
E. A diligent search for infections should be conducted and treated appropriately.
F. Patients should not be allowed to become hyperthermic.
G. All other toxic, metabolic, or structural causes of comas should be ruled out.

H. Vital signs, hematocrit, electrolytes, blood sugar, and serum osmolarity should be maintained within the normal range.

I. Seizures (25%): Fosphenytoin at 20 mg phenytoin equivalents/kg intravenously (IV) or intramuscularly (low risk of inducing hypotension and can be given intramuscularly if there is no IV access). Alternatively, phenytoin in the same doses can be given with careful blood pressure and cardiac monitoring. If serious acute underlying cardiac arrhythmias exist, IV phenobarbital is preferred. Intravenous valproate or intravenous levetiracetam is an alternate option, levetiracetam especially in cases where there is significant liver dysfunction.

J. EEG monitoring.

1. If seizures are controlled, a delayed EEG is done after 48 hours.
2. Continuous EEG monitoring is required for status epilepticus.

K. Controlling brain edema.

1. There is no role for the use of steroids or high-dose barbiturates, and hyperosmolar agents are seldom helpful in anoxic or hypoxic coma.
2. Controlled hyperventilation with a P_{CO_2} of 25 to 28 mm may be effective in the short term to avoid impending herniation.

L. Hypothermia: In two prospective randomized and controlled trials, induced hypothermia (IH) with rapid cooling to 33°C for 12 to 24 hours resulted in significant improvement in outcome after coma due to cardiac arrest compared with patients allowed to maintain normothermia. This is further supported by a meta-analysis of 5 randomized trials of 481 patients demonstrating improved outcome with IH. Increased vascular resistance, lactic acidosis, and decreased cardiac output were important complications. However, the incidence of cardiac arrhythmia was similar in the hypothermic and normothermic groups. Given these data, IH is currently considered the standard of care. Based on the published evidence to date, the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) Task Force has made the following recommendations: Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF). Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

M. Mobilization: Once coma begins to lighten, early mobilization should be the goal to prevent other complications.

VII. COMPLICATIONS

A. Delayed brain damage: Seen rarely, 3 to 30 days after the initial recovery, especially following carbon monoxide poisoning, a late functional decline occurs with irritability, lethargy, and increased muscle tone. Pathologically, widespread demyelination is found. Most patients survive this second insult.

B. Intention myoclonus is another delayed consequence. This can be distinguished from seizures by the absence of corresponding EEG changes.

C. Persistent vegetative state: No cortical function, although the patient appears awake and retains many bodily functions (feeding, sleep–wake cycle).

D. Brain death: The clinical criteria of brain death are defined in Chapters 15, 118 and 132. Total absence of electrocerebral activity, not associated with sedative hypnotic drugs or hypothermia, is helpful in confirming brain death in difficult cases. Similarly, a brain scan showing absence of blood flow is strongly suggestive of brain death.

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122 Status Epilepticus

Felicia C. Chu and Catherine A. Phillips

I. DEFINITIONS

A. *Status epilepticus* is defined as

1. One or more epileptic seizures lasting 30 minutes or longer without recovery between attacks (formal definition); or
2. Seizure activity lasting 5 minutes or longer (operational definition) without recovery between attacks.

B. *Myoclonic status* is repetitive, asynchronous myoclonic jerks typically in the setting of severe encephalopathy such as cerebral anoxia.

C. *Simple partial status* is continuous or repetitive focal seizures without loss of consciousness, such as focal motor seizures in *epilepsia partialis continua*.

D. *Nonconvulsive status* is a confusional state of 30 minutes or more.

1. *Absence status*: may have subtle myoclonic facial movements and automatisms of face and hands.
2. *Complex partial status*: either a series of complex partial seizures, separated by a confusional state, or a prolonged state of partial responsiveness and semipurposeful automatisms.

II. ETIOLOGY

A. Symptomatic status—status caused by a neurologic or metabolic insult—is more common than idiopathic status.

B. Status can be caused by stroke, anoxic brain injury, electrolyte disturbances (e.g., hyponatremia, hypomagnesemia, hypoglycemia, hyperglycemia, uremia, sepsis), drug or other toxicity, alcohol or other drug withdrawal, and decreasing antiepileptic medication.

C. Viral encephalitis from Epstein-Barr syndrome or herpes simplex virus can have an abrupt onset heralded by status epilepticus.

III. PROGNOSIS AND SEQUELAE

A. Overall, mortality rate is 7% to 25%. Advanced age, generalized tonic–clonic status epilepticus, depth of coma on presentation, and prolonged status (typically >24 hours) are poor prognostic factors.

B. Status caused by anoxia has the highest mortality rate followed by hemorrhage, tumor, metabolic disorders, and systemic infection. Status caused by alcohol withdrawal and antiepileptic drug discontinuation, and idiopathic status have lower mortality rates.

C. Long-term sequelae may include permanent focal neurologic deficits and chronic epilepsy. Aspiration pneumonia is a common complication of status.

IV. INITIAL ASSESSMENT, MANAGEMENT, AND MEDICAL STABILIZATION

A. Initial assessment and treatment should begin within 5 minutes of onset of seizure activity (Table 122-1).

B. History and exam: check for preexisting chronic seizure disorder, antiepileptic drug use, illicit drug use and trauma. Examine for focal neurologic abnormalities.

C. Status-induced hyperthermia will worsen neuronal injury and is essential to treat.

D. Metabolic acidosis often develops early in status and resolves spontaneously once seizures stop without treatment with bicarbonate.

E. When a metabolic disorder causes status, pharmacologic intervention alone is not effective.

F. Exclude systemic and central nervous system (CNS) infections; lumbar puncture (LP) is often necessary; leukocytosis, fever, and cerebrospinal fluid pleocytosis may be caused by status itself.

G. Only short-acting paralytic agents should be used; ongoing electroencephalogram (EEG) monitoring may be necessary for more continuous use.

H. Contrast-enhanced head computed tomography (CT) scan can be done after the patient has been stabilized and the seizures controlled. Magnetic resonance imaging (MRI) is preferred but often not practical in the emergent setting.

V. PHARMACOLOGIC MANAGEMENT OF GENERALIZED STATUS EPILEPTICUS

A. Goals: stop seizures early; prevent recurrence; try to determine the cause. Generalized convulsive status is a medical emergency.

B. A benzodiazepine drug is the initial therapy for status. Both diazepam and lorazepam have essentially the same cardiac (hypotension), respiratory (respiratory depression and apnea), and CNS-depressant side effects.

1. Lorazepam IV: 0.1 mg/kg at 2 mg/minute; a 2- to 4-mg dose may be given initially up to 0.2 mg/kg. The dose of diazepam is 0.15 mg/kg, additional 0.1 mg/kg if necessary.
2. Rectal diazepam is an alternative. For adults, 7.5 to 10 mg of the IV preparation or 0.2 mg/kg of the rectal gel preparation is administered per rectum (PR). The incidence of significant respiratory depression is lower with PR compared to IV administration.
3. Intramuscular (IM) absorption of these agents is delayed and incomplete; this route is unsuitable for treating status.
4. Midazolam IM can be effective if there is no IV access. For adults, 5 to 10 mg can be administered intramuscularly or rectally.

C. Phenytoin IV: 20 mg/kg IV load, 50 mg/minute. Give additional 5 mg/kg boluses of phenytoin to a maximum of 30 mg/kg, as needed. Do *not* give IM.

TABLE 122-1 Management Protocol for Generalized Status Epilepticus

Minutes: 0–10; first-line agents (benzodiazepines)

1. If diagnosis is uncertain, observe recurrence of generalized seizures without subsequent recovery of consciousness.
2. Simultaneously, assess cardiopulmonary status; establish airway; administer O_2; initiate cardiac monitoring.
3. Start an IV line for administration of normal saline (avoid dextrose solution with phenytoin).
4. Draw blood for complete blood count and differential, glucose, blood urea nitrogen, creatinine, electrolytes, calcium, liver function tests, antiepileptic drug levels, toxicology screen; perform bedside glucose determination.
5. Give glucose (D50) 50 mL and thiamine 100 mg IV if hypoglycemia (BG < 80) is present.
6. Monitor respirations, blood pressure, ECG, oximetry, and, if possible, EEG.
7. Give lorazepam (0.1 mg/kg) IV bolus, <2 mg/min (may use 2 mg initial dose, and complete dose as needed).

Minutes: 10–30; second-line agents (phenytoin [fosphenytoin], levetiracetam, valproate sodium)

1. Start phenytoin or fosphenytoin (20 mg/kg) IV, 50 mg/min (fosphenytoin 150 mg/min), with slower rate if hypotension develops.
   - **a.** Give additional boluses of phenytoin or fosphenytoin (5 mg/kg), to a maximum of 30 mg/kg, if patient is still having seizures.
2. If phenytoin is contraindicated, start one of the following agents:
   - **a.** Levetiracetam (20–30 mg/kg) IV, 2–5 mg/kg/min
   - **b.** Valproate sodium (20–40 mg/kg) IV, 3–6 mg/kg/min, may give additional 20 mg/kg 10 min after loading infusion.

Minutes: 30–90 refractory status epilepticus (IV propofol, IV midazolam, IV pentobarbital)

1. If status continues after phenytoin infusion is completed, may consider levetiracetam, or immediately start phenobarbital (20 mg/kg) IV at ≤100 mg/min; intubation is necessary either before or during phenobarbital infusion.
2. If status persists, induce coma using one of the agents listed below. Continuous EEG is needed to monitor seizure control and level of anesthesia. Monitor EEG hourly until burst-suppression pattern is present.
   a. Pentobarbital: 5 mg/kg IV load, given slowly; give additional 5 mg/kg boluses as necessary to produce burst-suppression pattern. Maintenance infusion of 0.5–5 mg/kg/h.
   b. Midazolam, 0.1–0.3 mg/kg IV load, infusion rate 0.05–2 mg/kg/h.
   c. Propofol, 1–5 mg/kg load, infusion rate 1–15 mg/kg/h.

12 h: Slowly withdraw medication at 12–24 h; if seizures recur, resume infusion for 24 h; then slowly taper off again; continue this process as necessary.

IV, intravenous; ECG, electrocardiogram; EEG, electroencephalogram.

1. Hypotension, electrocardiographic changes, and respiratory depression can occur. Cardiac monitoring should be performed and the drug given more slowly (25 mg/minute) in elderly patients or in those with a history of cardiac comorbidities.
2. Severe tissue injury can also occur if phenytoin extravasates into tissue.

D. Fosphenytoin IV or IM: a water-soluble prodrug of phenytoin, rapidly converted to phenytoin. Fosphenytoin should be used in place of phenytoin when IV access is not available or phenytoin is poorly tolerated at the infusion site.

1. Fosphenytoin may be used IV or IM.
2. Therapeutic phenytoin concentrations are attained in 10 minutes with rapid IV infusion and in 30 minutes with slower IV infusion or IM injection.
3. Fosphenytoin is dosed in "phenytoin equivalents" (PE) units (same as for phenytoin [load 20 mg/kg PE]); administered at rates up to 150 mg/ minute PE.
4. Cardiac monitoring is required with IV fosphenytoin.

E. Levetiracetam IV: may be used if there is an allergy to phenytoin or significant comorbidities (liver or cardiac dysfunction). A 20 to 30 mg/kg load is given at 2 to 5 mg/kg/min. The maintenance dose may be adjusted if renal function is impaired.

F. Valproate sodium IV: another alternative to phenytoin. Give 20 to 40 mg/kg IV at 3 to 6 mg/kg/min; an additional 20 mg/kg may be given 10 minutes after loading infusion.

1. Serious adverse effects may include hyperammonemia, pancreatitis, thrombocytopenia, and hepatotoxicity. A known teratogen.
2. For traumatic brain injury patients, consider alternative agent. May be beneficial for patients with glioblastoma multiforme.

G. Phenobarbital IV: is as effective as the combination of benzodiazepines and phenytoin for initial therapy, but CNS depression is a major side effect.

1. If status persists 10 minutes after phenytoin load is complete, IV phenobarbital may be given (10 mg/kg) as an initial dose, then repeated if seizures continue (up to 20 mg/kg, maximum infusion rate of 100 mg/minute).
2. *Respiratory depression is a major side effect*, especially if benzodiazepines have been used. Monitor respirations and ensure an adequate airway.
3. In some cases, treatment of the status proceeds directly to induction of anesthesia as described in subsequent text, without using phenobarbital.

H. Refractory status epilepticus. If status continues after full loading doses of phenytoin and phenobarbital, a drug-induced coma to suppress electrical seizure activity completely is indicated.

1. Intubate the patient; provide continuous hemodynamic monitoring. Pressors are frequently needed. Ileus is also common.
2. Simultaneous EEG monitoring is required to monitor electrical seizure activity and assess depth of anesthesia.

3. Barbiturates (e.g., pentobarbital), midazolam, and propofol are commonly used to achieve drug-induced coma. Phenobarbital is not used for this purpose because it causes very prolonged coma.
4. Drug dose is increased until a burst-suppression pattern (suppressions at least 10 seconds) is seen on the EEG. The coma should be deepened, at times to virtual electrocerebral silence, in order to terminate any electrical seizure activity present in the bursts.
5. Therapeutic levels of phenytoin and phenobarbital need to be maintained to successfully wean off anesthetic agents; levels should be done daily. Phenobarbital levels as high as 50 μg/mL may be needed if attempts to wean off anesthetic agents result in recurrent seizures.
6. Drug-induced coma is continued for 12 to 24 hours, and then anesthesia is withdrawn over 6 to 12 hours under EEG surveillance. If electrical seizures recur, the process is repeated for a longer period of time.
7. Due to the effects of midazolam tolerance, consider substituting a different drug (e.g., pentobarbital, propofol) if status is not terminated within 48 hours on a midazolam infusion.
8. Propofol infusion syndrome is a potentially fatal complication of protracted infusions (>48 hours at doses >5 mg/kg/h) resulting in cardiocirculatory collapse with lactic acidosis, hypertriglyceridemia, and rhabdomyolysis. Close monitoring of serum triglycerides and serum lactate is mandatory.
9. The following drugs have been used in treatment of refractory status epilepticus with reported efficacy:
   a. Topiramate NG/PO 300 to 1,600 mg/day, divided two to four times daily.
   b. Lacosamide IV 200 to 400 mg, 200 mg IV over 15 minutes.
   c. Lyrica NG/PO 375 mg/day, divided two to three times daily.
10. Ketogenic diet is an emerging nonpharmacologic treatment of refractory status. The high-fat and low-protein/carbohydrate diet is administered via nasogastric tube and subsequently induces a metabolic shift toward acidosis, resulting in ketonuria, which can be present within a few days of initiation of the diet. Successful treatment of refractory status with the ketogenic diet has been described.

VI. PHARMACOLOGIC MANAGEMENT OF PARTIAL AND ABSENCE STATUS EPILEPTICUS

A. In nonconvulsive or focal motor status, the diagnosis requires 30 minutes of continuous clinical (or electrical) seizure activity. When status epilepticus presents with a change in mental status only, an EEG is required for confirmation.

B. Absence status is not associated with the severe adverse sequelae of convulsive status, but should be treated promptly, using the same protocol as for generalized status but with longer time allotments for each phase of the protocol, particularly before the induction of generalized anesthesia.

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123 Cerebrovascular Disease

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I. GENERAL PRINCIPLES

A. Cerebrovascular disease includes the following:

1. Stroke caused by arterial thrombotic or embolic ischemia (IS).
2. Intracerebral hemorrhage (ICH) and extracerebral hemorrhage (EH) into the subarachnoid, subdural, and epidural spaces.

B. Admission to the intensive care unit (ICU) is often warranted because of the severity of the disease or institution of newer therapies.

C. This chapter focuses on ischemic cerebrovascular disease (ICVD) and ICH.

II. ICVD

A. Prognosis.

1. Altered sensorium (state of consciousness), conjugate gaze paresis, and early radiologic signs of *large* infarction predict a poor outcome.
2. Lacunar stroke has a better prognosis (70% to 80% recovery).
3. Transient ischemic attack (TIA) patients have a 5.5% chance of stroke within 48 hours and 10% risk of stroke within 30 days.

B. Etiology.

1. ICVD results from restriction of blood flow to the brain, usually because of arterial occlusion.
2. Cardioembolic stroke is due to ischemic/valvular heart disease, atrial fibrillation, or cardiomyopathy.
3. Atherothrombotic stroke is caused by occlusion of a large intra-/extracranial portion of the carotid/vertebrobasilar system from progressive stenosis and occlusion.
4. Lacunar stroke is due to small blood vessel occlusion.
5. Watershed territory strokes result from systemic hypotension, with resulting border zone infarction (areas between anterior and middle cerebral artery [MCA], or middle and posterior cerebral artery distributions).

C. Diagnosis.

1. History—helps to determine the type of stroke.
   a. Cardioembolic more common during the day with acute onset.
   b. Atherothrombotic more often during sleep.

c. Intracranial hemorrhage often starts with a headache, and deficit may progress for a considerable time.

d. TIA is defined as a neurologic/retinal deficit due to IS, followed by full recovery and lack of infarction on imaging studies.

2. Examination.

a. Aphasia, hemiparesis or hemiparesthesia, and monocular visual loss suggest carotid system IS.

b. Vertigo, cerebellar ataxia, and crossed deficits (ipsilateral cranial nerve and contralateral hemiparesis or hemianesthesia) suggest involvement of the vertebrobasilar system.

c. Pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, and dysarthria—clumsy hand syndrome—suggest the diagnosis of lacunar stroke.

3. Laboratory and radiologic evaluation.

a. *Neuroimaging*: An essential procedure!

i. To exclude ICH or subarachnoid hemorrhage.

ii. To select patients for acute thrombolytic therapy.

iii. Noncontrast head computed tomography (CT) usually does not demonstrate the region of infarction in the acute period (within 12 hours of onset). Diffusion-weighted magnetic resonance imaging (DW-MRI) can demonstrate ischemic lesions within minutes of onset, whereas perfusion imaging (PI) demonstrates the area at risk of eventual infarction. A diffusion-weighted perfusion imaging (DW-PI) mismatch demonstrates the penumbra (salvageable tissue). Perfusion computed tomography (CTP) and CT angiography (CTA) are accurate, faster, and, therefore, more practical when thrombolytic therapy is anticipated.

b. An *electrocardiogram* (ECG) and telemetry in all patients with IS: A 30-day cardiac event monitor/implantable long-term cardiac monitor at discharge in cryptogenic stroke, to look for atrial fibrillation.

c. *Echocardiography*, transesophageal echocardiogram in selected cases.

d. *Carotid ultrasound* and transcranial Doppler ultrasound are used in patients with contraindications to CTA or magnetic resonance angiography (MRA).

e. *Blood studies*, at a minimum, should include the following: a complete blood count (CBC), fasting lipids, blood glucose, and sCRP. Hypercoagulable workup and anticardiolipin antibodies may be obtained in younger patients or those with prior venous thrombosis, recurrent abortions, thrombocytopenia, and migraine (lupus antiphospholipid antibody anticoagulant syndrome).

D. Treatment.

1. Identify patients who are candidates for thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) (Table 123-1). Thrombolysis: 33% greater probability of being free of any disability; at 3 months, 10-fold *relative* increased risk of intracranial bleeding.

a. Patients presenting within 4.5 hours of onset of ischemic stroke should have an urgent CT scan to rule out hemorrhage and large

TABLE 123-1 Intravenous Thrombolytic Therapy for Acute Ischemic Stroke

A. Inclusion criteria

1. Age older than 18 y
2. Time from stroke onset <4.5 h

B. Exclusion criteria

Absolute contraindications

1. Evidence of intracranial hemorrhage on pretreatment CT
2. Active internal bleeding

Relative contraindications (at the discretion of the treating physician)

1. Known bleeding diathesis, including, but not limited to, the following:
   a. Platelet count < 100,000/mm^3
   b. Patient has received heparin within 48 h and has an elevated aPTT > 35 s
2. Current use of oral anticoagulants (e.g., warfarin sodium) or recent use with an INR > 1.6 or current use of new anticoagulants (Dabigatran, Apixaban, Rivaroxiban). Full-dose enoxaparin within 24 h
3. Within 3 mo, any significant intracranial surgery, serious head trauma, or previous stroke
4. Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT
5. Systolic arterial pressure > 185 mm Hg or diastolic arterial pressure > 110 mm Hg refractory to antihypertensive therapy
6. Known cerebral AVM, or aneurysm
7. Recent major intracranial hemorrhage
8. Only minor or rapidly improving stroke symptoms
9. Major surgery or serious trauma, excluding head trauma, in the previous 14 d
10. History of gastrointestinal or urinary tract hemorrhage within 21 d
11. Recent arterial puncture at a noncompressible site or recent lumbar puncture
12. Abnormal blood glucose (<50 or >400 mg/dL), with reversal of deficits with dextrose
13. Postmyocardial infarction pericarditis
14. Seizure at the time of onset of stroke (perform CT angiogram: if cerebral arterial occlusion is found, proceed to thrombolysis)
15. For rt-PA beyond 3 h, NIHSS > 24, previous stroke, and diabetes, as well as anticoagulants, are relative contraindications. Consent is preferable in all cases, but required beyond 3 h.

CT, computed tomography; aPTT, activated partial thromboplastin time; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator.

infarcts (greater than one-third of the MCA territory). CTA should be considered to evaluate for large vessel occlusion amenable to endovascular thrombectomy. CTP or MRI (DW-PI) may be helpful to define extent of ischemic penumbra.

b. In the absence of a large infarct, if CTP or DW-PI demonstrates a mismatch, there may be grounds to consider thrombolysis, later than 4.5 hours after onset of ischemic stroke. The DIFFUSE-2 trial demonstrated that intra-arterial interventions up to 12 hours in patients with a DWI-PI mismatch led to favorable 1- and 3-month outcomes compared to patients without a mismatch.

c. In patients with IS due to occlusion of the internal carotid, basilar, or proximal MCA, suggested by a high National Institutes of Health Stroke Scale (NIHSS) score and confirmed by CTA, intravenous thrombolysis can be initiated at community hospitals; however, rapid transfer to a tertiary hospital should be considered for possible intra-arterial endovascular thrombolysis or thrombectomy, which may be considered as a primary measure when it can be instituted without delay.

d. Written informed consent is desirable but not necessary in the first 3 hours as thrombolysis within the first 3 hours is considered standard of care (Table 123-1).

2. Blood pressure should be lowered to <185/110 mm Hg before thrombolytic therapy is initiated. For other patients, blood pressure can be observed in the absence of malignant hypertension; it should not be excessively lowered unless it exceeds 220/120 mm Hg or end-organ failure (congestive heart failure [CHF], renal) is present. If blood pressure has to be lowered acutely, the goal should be a 15% to 20% reduction.

3. Patients with limb paresis are at high risk of deep vein thrombosis, which can be prevented with pneumatic compression boots, subcutaneous heparin, or enoxaparin. In patients receiving rt-PA, initiation of prophylactic anticoagulant should be delayed for 24 hours.

4. Elevated temperature and hyperglycemia should be aggressively treated.

5. Oral feedings should be delayed until swallowing is deemed to be safe.

6. Cardioembolic stroke due to atrial fibrillation can be prevented with long-term anticoagulation using warfarin. Alternate drugs include thrombin inhibitors, factor Xa inhibitors, including dabigatran, apixaban, and rivaroxaban. Dabigatran using a dose of 150 mg twice daily is superior to warfarin with lower risk of spontaneous ICH. These newer anticoagulant drugs require no monitoring or dietary restrictions. The major disadvantage is lack of a reversal agent except with dialysis. There is no clear role for the use of full intravenous heparin or heparinoids in secondary stroke prevention or to improve outcome.

7. Antiplatelet therapy should be considered in patients who do not have a clear embolic source. Extended-release dipyridamole and aspirin (ERDP/ASA; Aggrenox) is FDA approved and is 23% more effective in reducing recurrent stroke compared with aspirin. The results for a recently completed international trial (PROFESS) suggests that clopidogrel may be as effective as ERDP/ASA).

8. High-dose statins may be beneficial within the first 48 hours due to pleiotropic effects. In the long term, statins should be administered to reduce low-density lipoprotein (LDL) cholesterol to <70 mg/dL. Antihypertensive therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor inhibitors (ARBs) further reduces risk of recurrent stroke by 30% to 40%.
9. Large strokes with worsening sensorium related to edema and raised intracranial pressure (ICP) are treated with short-term mannitol and, at times, with ICP monitoring. Early decompressive hemicraniectomy for large MCA stroke with altered sensorium is associated with a >50% absolute risk reduction in mortality, and >25% more patients achieve a better functional outcome.

III. ICH

A. General principles. ICH often requires management in the ICU. The leading cause is hypertensive ICH. Other causes are rupture of saccular aneurysms or arteriovenous malformations (AVMs), and cerebral amyloid angiopathy.

B. Prognosis. The prognosis for ICH is worse for larger lesions. Pontine ICH has the highest mortality, followed by cerebellar and then basal ganglia ICH. Lobar ICH carries the most favorable outlook for survival and functional recovery.

C. Etiology.

1. Hypertensive ICH results from rupture of arterial branch-point–acquired microaneurysm (Charcot-Bouchard aneurysms). Surrounding edema exerts a mass effect, and blood may block ventricles, causing hydrocephalus.
2. Nonhypertensive hemorrhage.
   a. Amyloid angiopathy.
   b. Rupture of AVM/aneurysm.
   c. Bleeding or coagulation disorders causing thrombocytopenia, loss of factors involved in coagulation (leukemia, idiopathic thrombocytopenia, severe liver disease, disseminated intravascular coagulation [DIC]), and other rare disorders of coagulation. Angiitis of the central nervous system and reversible cerebral vasoconstriction syndrome (RCVS) as well as venous thrombosis and dural fistulas are rare causes to consider.
   d. Anticoagulation and antiplatelet use.

D. Diagnosis.

1. History: The presentation of ICH is abrupt and often associated with headache and progressive neurologic deficits over minutes to hours.
2. Examination.
   a. Helpful clinical hints to suggest ICH include deficits that extend beyond the distribution of a single artery and presence of altered sensorium.

b. Localization.
- **i.** Putamen (hemiparesis, hemiesthesia).
- **ii.** Pons (hyperthermia, coma, pinpoint pupils).
- **iii.** Thalamus (hemihypesthesia, disconjugate vertical gaze).
- **iv.** Cerebellum (ataxia, nystagmus, head tilt, vomiting).
- **v.** Cerebral cortex (if cortical signs are present in a nonhypertensive ICH, suspect cerebral amyloid angiopathy).

3. Radiologic and laboratory tests.
- **a.** CT scan demonstrates the site and size of the hematoma with great accuracy.
- **b.** MRI is as sensitive to detect blood and may demonstrate underlying pathology such as a vascular malformation or tumor.
- **c.** Angiography should be considered if an underlying vascular malformation is suspected.
- **d.** Lumbar puncture is contraindicated in most cases of ICH because of the risk of transtentorial herniation.
- **e.** Coagulation profile and platelet count to exclude underlying bleeding disorder.

E. Treatment.

1. Correct any predisposing systemic hemorrhagic factors to prevent further clinical deterioration. Reverse warfarin-related bleeds with recombinant factor VII or prothrombin complex concentrate. Vitamin K 10 mg IV should always be given. Fresh frozen plasma is less useful because of the slow speed of reversal.

2. Lower systolic blood pressure in the acute phase of ICH to between 110 and 160 mm Hg. β-Blockers are the agents of choice. Intravenous nicardipine is a safe alternative. Vasodilators (e.g., nitroprusside [Nipride]) should be avoided, because they can promote cerebral edema and elevate ICP.

3. Acute increases in ICP may require hyperosmolar agents, such as mannitol. Treatment of ICH with steroids can be detrimental. Hyperventilation reduces ICP, but severe hypocapnia can result in diffuse cerebral vasoconstriction.

4. Elevation of ICP from hydrocephalus is treated with ventriculostomy.

5. Surgery may be indicated for large superficial lobar ICH and cerebellar ICHs. Early surgical intervention is indicated for lesions >2.5 cm associated with changes in mental status. Decompressive hemicraniectomy may be lifesaving, but the quality of life will depend on the extent of brain damage and potential for reversibility. Prophylactic anticonvulsants are not routinely used in ICH.

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124 Subarachnoid Hemorrhage

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I. GENERAL PRINCIPLES

A. Frequency and morbidity of subarachnoid hemorrhage (SAH).

1. Aneurysmal SAH accounts for 85% of nontraumatic SAH.
2. Perimesencephalic and other mechanisms of nontraumatic SAH account for the remaining 15% of cases and have lower incidences of morbidity and mortality from rebleeding and delayed ischemic deficits.
3. Intracranial hemorrhage secondary to the rupture of saccular aneurysms accounts for 2% to 5% of all new strokes and accounts for over 30,000 new cases in the United States annually.

B. Management of SAH caused by a ruptured aneurysm includes:

1. Early aneurysm repair to limit rebleeding.
2. Nimodipine to ameliorate cerebral injury secondary to vasospasm.
3. Hemodynamic and endovascular intervention to treat and overcome vasospasm.

II. PROGNOSIS. Prognostic indicators:

A. Unruptured aneurysms >10 mm in size and smaller aneurysms at the basilar tip are more likely to rupture as compared with smaller aneurysms in other locations.

B. Decerebration or coma at onset (Hunt and Hess grades 4 and 5) are associated with worse outcome.

C. Up to 51% of patients with SAH die, many before reaching medical care and most of the remainder in the first 2 weeks of care. Up to 33% of survivors need long-term care, and up to 46% of survivors suffer some form of long-term cognitive dysfunction.

III. PATHOGENESIS

A. Saccular (berry) aneurysms are distinguished from other types of intracerebral aneurysms caused by trauma, vascular dissection, or mycotic lesions and those related to tumors.

B. Of saccular aneurysms, 85% are located in the anterior circulation and 15% in the posterior circulation. Multiple aneurysms can occur in families or with systemic diseases such as polycystic kidney, Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, fibromuscular dysplasia, and coarctation of the aorta.

C. Risk factors include tobacco use, heavy alcohol use, cocaine abuse, hypertension, and history of intracranial aneurysm in a first-degree relative.

IV. DIAGNOSIS

A. History.

1. Severe headache that is usually described as the worst ever and maximum intensity at onset. Reversible vasoconstriction syndrome and benign exertional headaches can mimic SAH.
2. Sudden loss of consciousness, nausea, vomiting.
3. Facial pain, pupillary dilation and ptosis (from oculomotor nerve compression), and visual field defects (from optic nerve or chiasm compression).
4. A warning leak, or sentinel hemorrhage affects 15% to 37% of patients. Physicians should have a high index of suspicion for aneurysmal expansion or warning leak when patients present with sudden, maximal headache because such events precede major hemorrhage.

B. Examination.

1. Neck stiffness.
2. Altered sensorium.
3. Focal signs (hemiparesis, oculomotor palsy, visual loss, paraparesis).

C. Laboratory studies.

1. A noncontrast head computed tomography (CT) is used to identify, localize, and quantify the hemorrhage. Modern CT is over 98% sensitive for SAH on the first day of hemorrhage.
2. Lumbar puncture (LP) is indicated if CT is nondiagnostic in a case with strong clinical suspicion.
3. When CT and LP are negative, in some cases escalation to computed tomography angiography (CTA) or conventional catheter angiography may be performed.
4. If surgery is emergent, CT angiography is the preferred study.
5. Four-vessel cerebral angiography is the most precise imaging study to localize the aneurysm(s), define the vascular anatomy, and assess vasospasm. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) or CTA can be performed to reveal aneurysms larger than 4 mm.
   a. Imaging the upper cervical spine with angiography and MRI is important when cerebral angiography fails to reveal the source of hemorrhage.
   b. If the initial angiogram fails to demonstrate the source of SAH, angiography may be repeated in 1 to 2 weeks. If clinically stable, patients may be discharged home after the second negative angiogram. In some cases, a third angiogram may be performed in several months' time.

V. PREVENTION.

Prevention of SAH is possible by screening for aneurysm in high-risk populations (e.g., polycystic kidney disease) and reducing risk factors (e.g., smoking). Early surgery may be considered in some patients with asymptomatic aneurysms at high risk of rupture, which depends on size and location.

VI. TREATMENT

A. Management.

1. Preoperative medical management includes bed rest, head elevation to improve cerebral venous return, pulmonary toilet, thrombophlebitis prophylaxis, antiemetics, blood pressure control, and pain control.
2. Transfer to a center with neurosurgical expertise, preferably where a minimum of 60 SAH patients are treated annually, should be arranged rapidly as rebleeding and early hydrocephalus are important causes of morbidity.
3. Rebleeding is a serious complication of SAH, postulated to be caused by breakdown of the perianeurysmal clot. The peak incidence of rebleeding occurs during the first day after SAH, and one-half to two-thirds of patients who rebleed die. Key preventative measures include early repair of the aneurysm and blood pressure control.
4. Before aneurysm repair, systolic blood pressure is maintained below 160 mm Hg with β-blocking agents that also reduce the risks of cardiac arrhythmias. Nicardipine may be used when bradycardia exists. Nitrates are avoided due to their potential to raise intracranial pressure (ICP). No consensus exists on upper limits for blood pressure after aneurysm repair when vasospasm dominates morbidity; 200 to 220 mm Hg is a common limit. Some authors suggest treating hydrocephalus before significantly lowering blood pressure in case ICP is elevated so as not to compromise CPP.
5. Hypothalamic damage can cause cardiac dysrhythmias from excessive sympathetic stimulation. Myocardial ischemia may occur from increased sympathetic tone, as can global myocardial depression.
6. Hydrocephalus can develop within the first 24 hours after SAH because of impaired cerebrospinal fluid (CSF) resorption by the arachnoid granulations or intraventricular blood obstruction of CSF outflow. Ventricular drainage may be emergently indicated.
7. Anticonvulsant prophylaxis with phenytoin or levetiracetam is common. There is controversy over the necessary duration of therapy, and some data suggest worse cognitive outcomes for patients on long-term prophylaxis.
8. Steroids are frequently administered to limit inflammation at the arachnoid granulations and treat perioperative edema.
9. Hyponatremia can develop from hypothalamic dysfunction, causing a salt-wasting syndrome. This is commonly confused with syndrome of inappropriate antidiuretic hormone (SIADH); the two are distinguished by urine output and electrolyte levels. Hyponatremia is treated with isotonic or hypertonic saline. Fluid restriction is not indicated. Euvolemia is maintained throughout the hospital course.

B. Repair of ruptured aneurysm.

1. Surgical management is craniotomy with clip occlusion of the aneurysm neck, usually within 48 hours of rupture in most noncomatose patients.
   a. Unique problems that dictate the use of specialized techniques included vertebral–basilar system aneurysms, giant aneurysms (>25 mm), and multiple aneurysms.

b. Follow-up angiography is performed to evaluate occlusion of the aneurysm and patency of the surrounding vessels.

2. Endovascular repair includes coil embolization of appropriately shaped aneurysms.

a. Some lesions require balloon or stent-assisted techniques due to aneurysm morphology.

b. In cases where embolization and surgical clipping are not possible, balloon or coil occlusion of the parent artery may be considered.

3. Surgical clipping is definitive, but a higher percentage of patients may develop epilepsy post repair. Endovascular repair is less invasive, but patients may require multiple coilings due to aneurysm recanalization and patients have been reported to have higher incidence of vasospasm, possibly due to lack of drainage of blood during craniotomy or due to a selection bias.

C. Neurologic complications.

1. **Cerebral vasospasm** is a major cause of morbidity and mortality. Noted angiographically in 70% of patients, vasospasm causes symptoms because of cerebral ischemia in only 36% of cases. Vasospasm occurs progressively, with a peak between days 4 and 12. It occurs more frequently in patients with a poor clinical condition, thick focal blood clots, or a diffused layer of blood in the subarachnoid space. Neurologic deficits may be focal, correlated with the areas of cerebral ischemia; more global, cognitive deficits may signal distal microvascular ischemia. Vasospasm is diagnosed by angiography or noninvasively by Transcranial Doppler (TCD) that detects spasm in up to 50% of patients.

a. **Calcium antagonists.** The calcium antagonist nimodipine reduces delayed neurologic deficits caused by vasospasm. Nimodipine exerts a beneficial effect by decreasing postinjury intracellular calcium; dilating leptomeningeal vessels; improving collateral circulation to ischemic areas; improving erythrocyte deformability; or exerting an antiplatelet aggregating effect. Nimodipine (60 mg) is given orally every 4 hours for 21 days from the onset of SAH. If hypotension occurs, the dose is divided in half and administered every 2 hours.

b. HMG-CoA reductase inhibitors may decrease the incidence and severity of vasospasm. Simvastatin 80 mg daily has been shown to be safe and effective. A large multicenter trial is under way to quantify the benefit better.

c. **Hyperdynamic therapy.** The current mainstay of medical therapy for symptomatic vasospasm is hypertensive, hypervolemic therapy (HHT) to augment cerebral blood flow (CBF). Elevation of arterial pressure increases CBF; volume augmentation provides hemodilution, decreases viscosity, and improves cerebral microcirculation.

i. Criteria to initiate treatment include increased TCD blood flow velocity, focal neurologic deficits, or impaired consciousness without hydrocephalus.

ii. Vasopressors are used to keep systolic blood pressures elevated, and plasma volume is maintained with fluids and occasionally albumin.

iii. Hematocrit is often maintained at approximately 30, though controversy exists regarding the risk/benefit of transfusion to this goal.

iv. Risks of therapy include myocardial infarction, congestive heart failure, dysrhythmias, hemorrhagic infarcts, rebleeding, hyponatremia, and hemothorax.

d. Endovascular treatments for vasospasm may be employed when HHT fails. Options include intra-arterial injection of vasodilators such as nicardipine, verapamil, or milrinone. For proximal vessel vasospasm, balloon angioplasty may be performed.

e. Emerging technologies such as brain tissue oximetry, microdialysis, and CBF monitoring may in the future permit earlier detection and more targeted treatment of vasospasm.

2. Treatment of intracranial hypertension may require an ICP monitor and/or CSF drainage. Mannitol and hypertonic saline may be used, but strict attention to euvolemia is required.

3. Unresponsive patients should undergo electroencephalography (EEG) monitoring. Subclinical seizures have been reported in up to 20% of such cases.

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125 The Guillain-Barré Syndrome

Isabelita R. Bella and David A. Chad

I. GENERAL PRINCIPLES

A. Guillain-Barré syndrome (GBS) encompasses a group of acute immune-mediated polyneuropathies that present with rapidly progressive weakness, areflexia, and elevated cerebrospinal fluid (CSF) protein without pleocytosis.

B. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common subtype in North America and Europe, occurring at all ages and producing multifocal demyelination of nerve roots and cranial and peripheral nerves.

C. Axonal forms of GBS include acute motor axonal neuropathy (AMAN) and acute motor–sensory axonal neuropathy (AMSAN). AMAN is seen in children and young adults in northern China, Mexico, and Japan, is commonly preceded by *Campylobacter jejuni* infection, and generally has a good prognosis.

D. GBS is the most common cause of rapidly progressive sporadic weakness; 60% of patients recover fully, but 15% have major residual deficits and up to 5% succumb to respiratory, autonomic, and other complications of the illness.

II. DIAGNOSIS

A. Clinical features of AIDP.

1. The major clinical features of AIDP are rapidly evolving weakness (usually over days) and areflexia, heralded by dysesthesias of the feet or hands, or both.
   - **a.** Weakness classically ascends from legs to arms but may begin with weakness of cranial nerve–supplied muscles or of upper limb muscles and descend to the legs.
   - **b.** Proximal muscle involvement is often seen early in the course of the disease.
   - **c.** In severe cases, respiratory and bulbar muscles are affected.

2. Patients may become quadriparetic and respirator dependent within a few days, or they might have only mild nonprogressive weakness of the face and limbs throughout the course of the illness.

3. Weakness typically does not progress beyond 4 weeks.
   - **a.** Progression beyond 2 months is designated "chronic inflammatory demyelinating polyradiculoneuropathy" (CIDP), a disorder with a natural history different from GBS.
   - **b.** A small percentage (2% to 5%) of patients will have recurrent—two or more episodes—of GBS.

4. Approximately two-thirds of patients have an antecedent infectious event 1 to 3 weeks before the onset of GBS.
   a. Often there is a prodromal flu-like or diarrheal illness caused by a variety of infectious agents, including cytomegalovirus, Epstein-Barr and herpes simplex viruses, *Mycoplasma, Chlamydia*, and *C. jejuni.*
   b. GBS has also been associated with human immunodeficiency virus (HIV) infection, Hodgkin disease, systemic lupus erythematosus, immunization, general surgery, and renal transplantation. Lyme disease can mimic GBS.

B. Physical examination.

1. There is symmetric weakness in both proximal and distal muscle groups associated with attenuation or loss of deep tendon reflexes.
2. Objective sensory loss is usually mild.
3. Between 10% and 25% of patients require ventilator assistance within 18 days after onset. Patients must be followed carefully with serial vital capacity (VC) measurements until weakness has stopped progressing.
4. Mild-to-moderate bilateral facial weakness often occurs in addition to bulbar difficulties.
5. Ophthalmoparesis is unusual unless seen in the Miller Fisher variant (characterized by ophthalmoplegia, ataxia, and areflexia, with little limb weakness).
6. Autonomic nervous system disturbances are seen in more than 50% of patients and include cardiac arrhythmias, orthostatic hypotension, hypertension, transient bladder paralysis, increased or decreased sweating, and paralytic ileus.

C. Clinical features in axonal forms.

1. Patients with axonal forms (AMAN and AMSAN) present similarly to AIDP with rapidly progressive weakness, areflexia, and albuminocytologic dissociation, but they differ in the following ways:
   a. AMAN patients lack sensory abnormalities, and this form is more commonly found in northern China, Japan, and Mexico during summer months among children and young adults, is very commonly associated with prior *C. jejuni* infection, and has a good prognosis for recovery.
   b. AMSAN is generally associated with more pronounced deficits and longer time to recovery.

D. Laboratory studies.

1. Cerebrospinal fluid.
   a. An elevated CSF protein without an elevation in cells (albuminocytologic dissociation) is characteristic of GBS.
   b. CSF protein may be normal within the first 48 hours, but often is elevated within 1 week of onset; rarely, it remains normal several weeks after the onset of GBS.
   c. The cell count rarely exceeds 10 cells/cm^3 and is mononuclear in nature.

d. When GBS occurs as a manifestation of HIV infection or Lyme disease, the CSF white cell count is generally increased (25 to 50 cells).
e. The CSF glucose is always normal.

2. Electrodiagnostic studies in AIDP.
a. Typically disclose slowing (<80% of normal) of nerve conduction velocity, with prolonged distal motor and sensory latencies.
b. The amplitude of the evoked motor responses is typically reduced, and the form of the responses is often dispersed.
c. Early in the course of GBS, routine nerve conduction studies may be normal, with the exception of prolonged F wave responses and absent H reflexes. Another electrodiagnostic characteristic of the early phase of GBS is the preservation of the sural (sensory) response, in the face of reduced or absent upper extremity sensory responses (such as the median, ulnar, and radial). Early on, electromyography of a weak muscle will demonstrate decreased numbers of normal appearing motor unit potentials firing rapidly without fibrillation potentials.
d. Active denervation in the form of fibrillation potentials and positive sharp waves will first be seen 2 to 3 weeks after the onset of weakness if the pathophysiology of the neuropathy involves axon loss.

3. Electrodiagnostic studies in axonal forms.
a. In AMSAN, nerve conduction studies may reveal inexcitable motor and sensory nerves.
b. In AMAN, nerve conduction studies reveal low amplitude to absent motor responses with normal sensory responses and normal conduction velocities.
c. Three weeks after the onset of weakness, needle examination may reveal signs of denervation in both axonal forms.
d. The electrodiagnostic findings in the Miller Fisher syndrome are indicative of a sensory neuronopathy with reduced or absent sensory responses throughout in the face of normal motor studies.

4. Autoantibodies to glyconjugates.
a. Approximately 90% of Miller Fisher syndrome patients have high titers of ganglioside (GQ1b) antibodies.
b. Antibodies to GD1a, GM1, GM1b, and GalNac-GD1a are associated with the axonal forms of GBS. Anti-GM1 antibodies are reported in 10% to 42% AMAN patients.

E. Differential diagnosis.

1. A number of conditions causing rapidly progressive weakness must be differentiated from GBS.
a. Neuromuscular junction disorders: myasthenia gravis and botulism.
b. Disorders of peripheral nerve: tick paralysis, shellfish poisoning, toxic neuropathy, acute intermittent porphyria, diphtheritic neuropathy, and critical illness polyneuropathy.
c. Motor neuron disorders: amyotrophic lateral sclerosis, poliomyelitis, West Nile virus.
d. Disorders of muscle: periodic paralysis, metabolic myopathies, inflammatory myopathies, and critical illness myopathy if the patient is in intensive care.

III. PATHOGENESIS

A. AIDP is thought to be produced by immunologically mediated demyelination of the peripheral nervous system.

1. It is likely that both humoral and cellular components play a role.
2. In AIDP, the immune attack appears to be directed to epitopes on the Schwann cell, but the exact antigens have not been identified.

B. In axonal forms, the immune response is targeted toward epitopes on the axolemma.

1. Gangliosides GD1a, GM1, GM1b, and GalNac-GD1a may be the epitopes targeted in the immune response.
2. Anti-GM1 antibodies may cause conduction failure by disrupting voltage-gated sodium channels at the nodes of Ranvier.

C. The concept of molecular mimicry, in which an immune attack occurs on the epitope shared by the nerve fiber and infectious organism, is thought to be a possible mechanism for *C. jejuni*–associated GBS.

D. Pathologic studies in AIDP have usually shown endoneurial mononuclear cellular infiltration with a predilection for perivenular regions and segmental demyelination. The inflammatory process occurs throughout the length of the nerve (from the level of the root to distal nerve twigs).

IV. TREATMENT

A. Close observation for potential respiratory and autonomic nervous system dysfunction is required, preferably in an intensive care unit (ICU).

1. Forced VC and maximal inspiratory pressure (MIP) should be followed at frequent intervals.
2. A baseline arterial blood gas should be obtained.
3. Ropper and Kehne suggest intubation if any one of the following criteria is met:
   - **a.** Mechanical ventilatory failure with reduced VC of 12 to 15 mL/kg.
   - **b.** Oropharyngeal paresis with aspiration.
   - **c.** Falling VC over 4 to 6 hours.
   - **d.** Clinical signs of respiratory fatigue at a VC of 15 mL/kg.
4. Consider elective intubation in those with respiratory factors highly associated with progression to respiratory failure.
   - **a.** VC < 20 mL/kg.
   - **b.** MIP < 30 cm H_2O.
   - **c.** Maximal expiratory pressure (MEP) < 40 cm H_2O.
   - **d.** A reduction of >30% of VC, MIP, or MEP in 24 hours.
5. Tracheostomy should not be performed at the outset of the disease because patients can improve rapidly.

B. Because of potential autonomic dysfunction, careful monitoring of blood pressure, fluid status, and cardiac rhythm is essential in managing patients with GBS. Hypertension can be managed with short-acting agents such as labetolol or nitroprusside, hypotension with fluids, and bradyarrhythmias with atropine.

C. Immunotherapy with plasmapheresis (PE) or intravenous immune globulin (IVIG) is recommended for those patients who are nonambulatory and present within 4 weeks of symptom onset. PE or IVIG is also suggested for those patients who are ambulatory but not recovered within 4 weeks of symptom onset. For those patients who have only mild symptoms and are already recovering, immunotherapy is not recommended.

1. Although both PE and IVIG are equally efficacious, IVIG is more commonly used as the initial treatment because it is easier to administer.
2. Plasmapheresis:
   - **a.** GBS study group recommends exchanging 200 to 250 mL/kg in three to five sessions over 7 to 14 days.
   - **b.** Requires good venous access and can induce hypotension; requires caution in patients with cardiovascular disease.
3. IVIG:
   - **a.** Dose administered is 400 mg/kg/d for 5 consecutive days.
   - **b.** Easier to administer but can produce side effects such as flu-like symptoms, headache, and malaise.
   - **c.** Should be avoided in patients with immunoglobulin A (IgA) deficiency and renal insufficiency.
4. Corticosteroids have no role in the treatment of GBS.
5. Treatment with PE followed by IVIG has not been found to be superior to either treatment used alone.

V. OUTCOMES

A. Most patients recover over weeks to months.

B. At 1 year, approximately 60% recover full motor strength, while 14% have severe motor problems. About 5% to 10% have a protracted course, are ventilator dependent for several months, and do not fully recover.

C. Poor prognostic factors include those with electrodiagnostic evidence of axon loss, a higher disability grade at nadir, older age, and rapid onset of disease.

D. Despite close monitoring in the ICU, approximately 5% of patients die.

E. Causes of fatal outcomes include dysautonomia, sepsis, acute respiratory distress syndrome, and pulmonary emboli.

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126 Myasthenia Gravis

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I. GENERAL PRINCIPLES

A. Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and exaggerated muscle fatigue.

B. Prevalence is between 10 and 20 per 100,000 with a 3:2 female-to-male predominance.

C. Incidence in women peaks in the third decade and in men in the fifth to sixth decades.

D. Oculomotor and bulbar muscles are most commonly affected; proximal muscles are usually more affected than distal muscles; variability over time in both severity and distribution of weakness is common.

E. About 20% of patients with generalized MG experience myasthenic crisis, which reflects severe bulbar and respiratory muscle weakness, constituting a medical emergency and requiring intensive care.

F. Factors commonly associated with myasthenic crisis include systemic infection, electrolyte imbalance, anesthesia, and drugs that impair neuromuscular transmission (Tables 126-1 and 126-2).

II. PATHOPHYSIOLOGY

A. Circulating autoantibodies bind with acetylcholine receptors in postsynaptic muscle membrane.

B. Receptors may be blocked, and receptor density decreases due to accelerated degradation and turnover.

C. Miniature end-plate potentials are normal in number (indicating normal quantal release of acetylcholine) but decreased in amplitude.

III. PROGNOSIS

A. Available therapies offer effective treatment for the vast majority of patients.

B. Aggressive airway management and respiratory support during myasthenic crisis minimize morbidity and mortality with current mortality rate <5%.

C. Elective thymectomy favorably alters the natural history of the disease.

IV. DIAGNOSIS

A. Clinical presentation.

1. MG should be considered in any patient with unexplained weakness, especially when weakness fluctuates or involves bulbar muscles.

TABLE 126-1 Conditions That May Contribute to Myasthenic Crisis

Intercurrent systemic infection
Electrolyte imbalance (Na, K, Ca, P, Mg)
Thyrotoxicosis or hypothyroidism
Anesthesia
Medication effects (Table 126-2)
Cholinergic crisis (discontinue cholinesterase inhibitors)

2. Normal sensation, tendon reflexes, pupillary reflexes, and mental status distinguish MG from most other acute and subacute paralytic illnesses.

B. Antiacetylcholine receptor antibodies.

1. Eighty percent of patients have serum antibodies to acetylcholine receptors.
2. Among "seronegative" patients, about 40% will have anti–muscle-specific tyrosine kinase (MuSK) antibodies.

TABLE 126-2 Medications That May Accentuate Myasthenic Weakness

Antibiotics
Amikacin
Clindamycin
Colistin
Fluoroquinolones
Gentamicin
Neomycin
Polymyxin
Streptomycin
Tobramycin
Tetracyclines
Trimethoprim/sulfamethoxazole

Antiarrhythmics and antihypertensives
Lidocaine
Quinidine
Procainamide
β-Blockers
Calcium channel blockers

Antipsychotics
Lithium
Phenothiazines
Tricyclics

Neuromuscular blockers and muscle relaxants
Anectine (succinylcholine)
Norcuron (vecuronium)
Pavulon (pancuronium)
Tacrium (atracurium)
Benzodiazepines
Curare
Dantrium (dantrolene)
Flexeril (cyclobenzaprine)
Lioresal (baclofen)
Robaxin (methocarbamol)
Soma (carisoprodol)
Quinine sulfate

Antirheumatics
Chloroquine
D-penicillamine

Others
Opiate analgesics
Oral contraceptives
Antihistamines
Anticholinergics

C. Edrophonium (Enlon) test.

1. Useful in patients with objective findings on physical examination.
2. May be performed at bedside; monitor for bradyarrhythmia.
3. Not as sensitive or specific as the serological and electrodiagnostic studies.

D. Electrodiagnostic studies.

1. Decrement (≥10%) in compound muscle action potential amplitude with 2 to 3 Hz repetitive supramaximal stimulation.
2. Increased "jitter" on single-fiber electromyography (EMG).
3. Electrodiagnostic studies may support—but never exclude—the diagnosis of MG.

E. Chest imaging: All patients with MG should be screened for thymic hyperplasia or thymoma.

V. TREATMENT. Immunosuppressive therapy is indicated for most patients with MG, but benefits are often delayed. Plasmapheresis and intravenous immune globulin (IVIG) offer a more rapid, but transitory, benefit (Table 126-3). Cholinesterase inhibition is a useful adjunctive therapy.

A. Plasmapheresis.

1. Exchange 50 mL/kg/d for 3 to 7 days.
2. Response within 48 to 72 hours.

B. IVIG.

1. 400 mg/kg/d for 5 days.
2. Response within 7 to 10 days.

C. Corticosteroids.

1. Response rate >80%.
2. 20 mg/day (single dose), increasing by 5 mg/day every 3rd day to 60 to 80 mg/day.
3. Beware of increased weakness at the outset of steroid treatment.
4. After maximal response (2 to 3 months), gradually shift to equivalent alternate day dose; then taper slowly by decreasing alternate day dose by 5 mg each month to 20 mg every other day target.

TABLE 126-3 Management of Myasthenic Crisis

Airway assistance and ventilation
Discontinue anticholinesterases and offending medication
Identify and treat infection
Cardiac monitor
Start specific treatment (see below)
  Plasmapheresis: exchange 50 mL/kg/d for 3 to 7 d
  IVIG: 400 mg/kg/d for 5 d
  Corticosteroids: 20 mg/d (single dose), increasing by 5 mg/d every 3rd d to 60 to 80 mg/d

5. Complete discontinuation, with maintained response, is rare; *avoid stopping prednisone!*
6. Azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, and other immunosuppressants can be considered in patients who are steroid intolerant or unresponsive.

D. Cholinesterase inhibition.

1. Pyridostigmine (Mestinon) and neostigmine (Prostigmine) are useful adjuncts.
2. Conversion of PO pyridostigmine: IV pyridostigmine is 30:1 (may be useful following surgery).
3. Cholinergic crisis is increased weakness due to excess cholinergic stimulation; fasciculation, diaphoresis, and diarrhea are concomitants.

E. Supportive care in the intensive care unit (ICU) and recovery room.

1. Avoid incentive spirometry and magnesium boluses.
2. Maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and forced vital capacity (FVC) are the best indicators of respiratory muscle function; O_2 saturation is a poor indicator.
3. Early intubation is prudent in the event of declining respiratory muscle function; consider mechanical ventilation when the FVC declines to 15 mL/kg.
4. Cholinesterase inhibition (pyridostigmine) will increase oral and airway secretions.

F. Thymectomy: Elective thymectomy through median sternotomy is indicated for all but the most elderly, frail myasthenic patients. Results are best when done within 5 years of onset.

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127 Acquired Weakness in the Intensive Care Unit

David A. Chad

I. GENERAL PRINCIPLES

A. A large prospective cohort study found the incidence of severe acquired weakness in the intensive care unit (ICU) to be 25%.

B. Although preexisting neuromuscular disorders may cause weakness in ICU patients, two of the most common causes of *newly acquired* weakness arising in the ICU setting are critical illness myopathy (CIM) and critical illness polyneuropathy (CIP).

C. Both disorders may cause severe generalized weakness—a syndrome of flaccid, generalized weakness (quadriplegia) with failure to wean from mechanical ventilation. The two disorders are known to occur separately or in combination. The most common form of weakness acquired in the ICU is CIM.

D. A major risk factor for the development of CIM is exposure to intravenous corticosteroids (CSs) and neuromuscular blocking agents (NMBAs); CIM develops in one-third of patients treated for status asthmaticus in the ICU.

E. CIM also develops in patients who have not received CS and NMBAs, but who have had severe systemic illness with multiorgan failure and sepsis; in fact, CIM accounts for 42% of patients with weakness in the surgical and medical ICU setting.

F. The major risk factors for CIP are sepsis and multiorgan failure; of patients admitted to the ICU for at least 2 weeks, 50% show at least EMG evidence of an axon loss polyneuropathy.

II. DIAGNOSIS OF CRITICAL ILLNESS MYOPATHY

A. Clinical features.

1. Weakness is typically widespread and nonfocal.
2. Weakness affects all limb muscles and neck flexors—a flaccid quadriparesis that has a proximal > distal distribution.
3. Weakness may involve facial muscles, but extraocular muscles are rarely involved.
4. Tendon reflexes are often depressed or absent.
5. Weakness typically affects the diaphragm, causing failure to wean from ventilator.

B. Laboratory studies.

1. Serum creatine kinase (CK) is elevated in 50% of patients; the rise tends to occur early in the course of the illness.
2. Electromyography.
   a. Nerve conduction studies reveal low-amplitude, long-duration (broad) responses, or absent motor responses; sensory responses are relatively preserved (sensory responses may be reduced).
   b. The needle electrode examination discloses fibrillation potential activity in weak muscles in some, but not all, patients.
   c. Voluntary muscle contraction reveals early recruitment of motor unit potentials (MUPs) that may be short in duration, low in amplitude, and polyphasic in form.
   d. MUP analysis is difficult owing to severe weakness or encephalopathy, or both (no motor units may be available for analysis).
   e. Stimulation of the phrenic nerves with diaphragm recording evokes absent or very low motor responses.
   f. Direct stimulation of a weak limb muscle may demonstrate electrical inexcitability of the muscle membrane.
   g. Direct stimulation of muscle and direct nerve stimulation yield comparably reduced muscle responses (in contrast to the results found in CIP [vide infra]).
3. Muscle biopsy.
   a. Reveals a characteristic finding of selective loss of myosin, which is revealed as a central area of pallor or lack of histochemical reactivity to myosin ATPase.
   b. Muscle fiber atrophy (especially type II fibers).
   c. Mild-to-moderate degree of muscle fiber necrosis in some patients.

C. Pathogenesis.

1. Loss of myosin thick filaments, with multifactorial causation, including an increase in muscle apoptosis, up-regulation of calpain, and up-regulation of the transforming growth factor (TGF)-β/mitogen-activated protein kinase pathway.
2. Muscle is noted to be inexcitable in CIM. This may result from improper regulation of the sodium channels with increased inactivation of sodium channels at the resting membrane potential.

D. Treatment.

1. Treatment is essentially symptomatic.
2. Strive to prevent the development of this disorder by using CSs or NMBAs, or both as sparingly as possible.
3. Intensive insulin therapy (with target blood glucose concentrations of 80 to 110 mg/dL) may lower the incidence of CIM (and CIP).

E. Outcome.

1. Most patients recover over weeks to months, although patients may be left with residual weakness depending upon the initial severity and duration of weakness.

III. DIAGNOSIS OF CRITICAL ILLNESS POLYNEUROPATHY

A. Clinical features.

1. Distal more than proximal symmetrical weakness *and* sensory loss.
2. Deep tendon reflexes are attenuated or lost.
3. Cranial nerve–innervated muscles are typically spared.
4. There is often a concomitant encephalopathy (the encephalopathy of sepsis).

B. Laboratory studies.

1. Serum CK levels are typically normal.
2. CSF studies are normal (normal protein and normal cell count).
3. Electromyography.
   a. Nerve conduction studies reveal reduced or absent sensory and motor responses and reduced or absent phrenic motor responses.
   b. Nerve conduction *velocities* are within the range of normal or are mildly reduced (the pattern considered classical for polyneuropathies that are primarily axon loss in character). There is typically no evidence for partial conduction block or prolonged F-wave latencies.
   c. After 2 to 3 weeks of the illness, needle electrode examination may reveal abnormal insertional activity in the form of fibrillation potentials and positive sharp waves; and these are more likely to be found in distal rather than proximal muscles; in the first 2 to 3 weeks of the illness, fibrillation potentials may be absent.
   d. Voluntary activation may reveal reduced recruitment of MUPs; in the first few weeks of the illness, MUPs may have a normal appearance, but after several months, as is typical of resolving polyneuropathies characterized by axonal regeneration, collateral sprouting, and muscle reinnervation, MUPs typically become complex or polyphasic in form, and increased in size.
   e. Direct needle stimulation of muscle elicits a relatively higher amplitude response compared to the response recorded from muscle after nerve stimulation.
4. Muscle biopsy.
   a. Neurogenic atrophy.

C. Pathogenesis.

1. Inadequate perfusion of peripheral nerves as a result of the systemic inflammatory response that causes injury to the microcirculation of distal nerves and resultant nerve ischemia and axon loss.
2. As in CIM, there is evidence for dysregulation of sodium channel gating in peripheral nerve that could lead to nerve inexcitability and contribute to generalized weakness.

D. Treatment.

1. Attempt to stabilize and treat the underlying critical illness; especially vigorous treatment of sepsis.
2. Intensive insulin therapy (with target blood glucose concentrations of 80 to 110 mg/dL) may lower the incidence of CIP.

E. Outcomes.

1. Recovery of sensory and motor function occurs over weeks to months depending on the severity of the underlying polyneuropathy.

IV. DIFFERENTIAL DIAGNOSIS OF ACQUIRED WEAKNESS IN THE ICU

A. Guillain-Barré syndrome (see Chapter 125).

B. Acute intermittent porphyric neuropathy.

1. Generalized weakness (symmetrical or asymmetrical) in the context of abdominal pain, psychiatric disorder, and prominent dysautonomia.
2. Triggered by drugs that induce the hepatic cytochrome P-450 system (e.g., barbiturates).
3. May be associated with respiratory failure.
4. EMG: Marked motor axon loss–type polyneuropathy without conduction block.
5. Diagnosis suggested by the presence of urinary porphyrin precursors, notably δ-aminolevulinic acid.
6. Responds to oral or parenteral carbohydrate loading and to IV hematin therapy.

C. Prolonged neuromuscular blockade by muscle relaxants.

1. Associated with renal or hepatic failure.
2. Elevated levels of vecuronium metabolite in some instances (3-desacetyl vecuronium).
3. No sensory deficits and normal reflexes.
4. Normal sensory and motor nerve conduction studies.
5. On EMG, decremental response at slow rates of stimulation (3 Hz).
6. Transient improvement after infusion of acetylcholinesterase inhibitors.

D. Myasthenia gravis (see Chapter 126).

E. Lambert-Eaton myasthenic syndrome.

1. Generalized weakness with autonomic symptoms and signs.
2. Strength typically *improves* after repetitive contractions of an initially weak muscle.
3. About 50% of patients have an underlying neoplasm (typically small cell lung cancer).
4. Presence of antibody to voltage-gated calcium channels in 80% of patients.
5. EMG: very low amplitude motor responses that increase after a short burst (10 seconds) of isometric exercise; sensory studies are normal.

F. Botulism.

1. Diffuse, symmetrical weakness; proximal greater than distal muscle involvement.
2. Cranial nerve involvement.
3. Dysarthria and dysphagia.
4. Ptosis and ophthalmoparesis.
5. Autonomic involvement.
6. Dilated pupils.

7. Bradyarrhythmias.
8. Hypotension.
9. Urinary retention.
10. Management is supportive care and trivalent (ABE) antitoxin.

G. Motor neuron disease (amyotrophic lateral sclerosis).

1. Scenario: an ICU patient admitted for pneumonia and ventilator support who fails to wean.
2. The examination classically reveals a combination of lower and upper motor neuron signs (atrophy/fasciculations and hyperreflexia/spasticity/Babinski signs, respectively) in bulbar (especially tongue and palate) and limb muscles (often asymmetric, distal and proximal), with a normal sensory examination.

H. Muscular dystrophies: uncommon scenario, but patients with certain muscular dystrophies are prone to respiratory muscle involvement and pneumonia. These include the following:

1. Myotonic dystrophy.
   a. Percussion and grip myotonia.
   b. Frontal balding/temporalis muscle atrophy.
   c. Distal muscle weakness and wasting.
   d. Cardiac conduction defects, especially atrial arrhythmias with risk of complete heart block.
   e. Central hypoventilation.
2. Duchenne and Becker dystrophy (X-linked dystrophy—dystrophinopathy).
   a. Calf pseudohypertrophy.
   b. Severe generalized weakness and wheelchair before age 12 (Duchenne); mild-to-moderate generalized weakness with ambulation to at least age 16 (Becker).
   c. Cardiomyopathy (targeting posterior wall of the left ventricle).
   d. Elevated CK (10 to 50 times above normal).
3. Congenital myopathy (severe forms of nemaline rod and centronuclear).

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128 Neuro-Oncological Problems in the Intensive Care Unit

Mayur Jayarao and N. Scott Litofsky

I. OVERVIEW:

Patients with primary or metastatic tumors may present with the following:

- **A.** Increased intracranial pressure (ICP).
- **B.** Hydrocephalus.
- **C.** Seizures.
- **D.** Postoperative complications.
- **E.** Spinal tumors.
- **F.** Systemic complications secondary to brain tumors.

II. INCREASED ICP

A. Background: Increased volume in a closed intracranial space causes increased pressure (Monro-Kellie doctrine).

B. Pathophysiology.

1. Tumor mass.
2. Hemorrhage.
3. Secondary cerebral edema adjacent to lesion.
4. Hydrocephalus.
5. Hypercarbia.
6. Cerebral ischemia.

C. Diagnosis.

1. **Clinical presentation.**
   - **a.** Headache.
   - **b.** Vomiting.
   - **c.** Papilledema: chronic finding of ICP elevation.
   - **d.** Decreased consciousness.
   - **e.** Cognitive changes.
   - **f.** Pupillary dilatation.
   - **g.** Diplopia.
   - **h.** Cushing triad.
     - **i.** Systolic hypertension.
     - **ii.** Bradycardia.
     - **iii.** Respiratory depression.

2. **Radiologic studies.**
   a. Magnetic resonance imaging (MRI): Better resolution than computed tomography (CT).
   b. CT: More available than MRI.

D. Treatment of intracranial mass effect and elevated ICP.

1. Head elevation >30 degrees.
2. Fluid restriction (slight).
3. Hyperosmolar therapy (hold if serum osmolality >320 mOsm/kg).
   a. Agents.
      i. Mannitol 1 to 1.5 g/kg IV bolus initially, then 0.25 to 0.5 g/kg every 4 to 6 hours.
      ii. Thirty to fifty milliliters 23.4% NaCl bolus, then 30-mL bolus every 4 to 6 hours.
      iii. Three percent hypertonic saline at 30 to 100 mL/h, titrated to a serum sodium goal of approximately 155 mEq/dL.
   b. Caveats.
      i. Use only one agent at a time.
      ii. Close monitoring of renal function and electrolytes.
4. Furosemide 1 mg/kg IV single dose or as 10 to 20 mg adjunct with mannitol.
5. Dexamethasone 10 to 20 mg IV initially, then 4 mg every 6 hours.
6. ICP monitoring (external ventricular drain [ventriculostomy] preferred).
7. Hyperventilation (for short periods only) to achieve $Paco_2$ 25 to 32 mm Hg.

III. HYDROCEPHALUS

A. Background: Increased ventricular size due to increased CSF volume and pressure.

B. Pathophysiology/etiology.

1. Subarachnoid tumor.
   a. Leptomeningeal tumor infiltration in subarachnoid space can prevent normal absorption of CSF by arachnoid granulations.
2. Cerebellopontine angle tumors: compress brainstem and fourth ventricle.
3. Intraventricular tumors: obstruct outflow foramen.
4. Intraparenchymal tumors.
   a. Basal ganglia and thalamic tumors: compress foramen of Monro.
   b. Pineal region tumors: compress third ventricle or cerebral aqueduct.
   c. Brainstem or cerebellar tumors: compress fourth ventricle or cerebral aqueduct.

C. Diagnosis.

1. **Clinical presentation:** Increased ICP (see Section II).
2. **Radiologic studies:** CT more readily available while MRI demonstrates better detail.

D. Treatment.

1. Dexamethasone 10 to 20 mg IV initially, then 4 mg every 6 hours.
2. External ventricular drain.
3. Tumor resection.
4. CSF diversion either internally (third ventriculostomy) or externally (shunt).

IV. SEIZURES

A. Background: May precipitate rapid deterioration when ICP is elevated.

B. Pathophysiology/etiology.

1. Tumor presence or progression.
2. Hemorrhage.
3. Hypoxia.
4. Hyponatremia.
5. Hypoglycemia.
6. Subtherapeutic anticonvulsant levels.

C. Diagnosis.

1. **Clinical presentation.**
   a. Variable: generalized, tonic–clonic, partial, focal or transient dysfunction.
2. **Radiologic studies:** CT scan.
3. **Laboratory studies:**
   a. Anticonvulsant levels (when applicable).
   b. Serum electrolytes.
   c. Arterial blood gas.

D. Treatment.

1. Airway management.
   a. If mechanically ventilated: maintain normocarbia.
2. Acute anticonvulsants.
   a. Lorazepam: 2 mg every 5 minutes IV (8 mg maximum for status epilepticus).
   b. Phenytoin.
      i. Loading dose: 15 to 20 mg/kg IV.
      ii. Maintenance: 100 mg IV/PO every 8 hours (serum goal 10 to 20 μg/mL).
   c. Fosphenytoin.
      i. Loading dose: 15 to 20 mg/kg IV.
      ii. Maintenance: 5 mg/kg/d (serum goal 10 to 20 μg/mL).
      iii. Phenobarbital: 15 mg/kg IV.
3. Prophylactic anticonvulsants.
   a. Levetiracetam.
   b. Phenytoin.
   c. Fosphenytoin.
   d. Carbamazepine.
   e. Phenobarbital.

V. POSTOPERATIVE COMPLICATIONS

A. Diagnosis.

1. **Clinical presentation.**
   - **a.** Headache.
   - **b.** Neurologic deficit.
   - **c.** Fever.
   - **d.** Polyuria/polydipsia.
2. **Etiology.**
   - **a.** Intracranial hemorrhage.
     - **i.** Risk factors: coagulopathy, hypertension.
   - **b.** Cerebral edema.
   - **c.** Cerebral infarction.
   - **d.** Endocrinopathies.
     - **i.** Diabetes insipidus (DI).
       - **(a)** May be transient, permanent, or triphasic.
       - **(b)** Usually 18 to 36 hours postoperatively.
       - **(c)** Greater than 250 mL/hour urine output for 2 consecutive hours.
       - **(d)** Urine specific gravity < 1.005 and urine osmolality < 200 mOsm/kg.
       - **(e)** Urine sodium > 145 mEq/L and serum osmolality > 290 mOsm/kg.
     - **ii.** Hypocortisolemia.
     - **iii.** Hypothyroidism.
     - **iv.** Hyponatremia.
       - **(a)** Usually from syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
       - **(b)** Cerebral salt wasting (CSW) uncommon with neoplastic processes.
     - **v.** Central nervous system infection.
       - **(a)** Meningitis: usually 2 days to 2 weeks postoperatively.
       - **(b)** Cerebral abscess: uncommon, presents weeks to months postoperatively.
       - **(c)** Bone flap infection: presents months postoperatively.
3. **Radiologic studies:** CT or MRI with and without contrast.
4. **Laboratory studies.**
   - **a.** Serum electrolytes and osmolality.
   - **b.** Complete blood count.
   - **c.** Erythrocyte sedimentation rate, C-reactive protein.
   - **d.** Hormone levels.
   - **e.** Urine specific gravity, electrolytes, and osmolality.
   - **f.** CSF chemistries, Gram stain, and culture.

B. Treatment.

1. Intracranial hemorrhage.
   - **a.** Correct coagulopathy (maintain INR ≤ 1.3, platelets ≥ 100,000 mm^3).
   - **b.** Systolic blood pressure 110 to 150 mm Hg.

2. Cerebral edema.
   a. Hyperventilation.
   b. Dexamethasone.
   c. Hyperosmolar therapy.
3. Cerebral infarction.
   a. Maintain cerebral perfusion.
   b. Treat symptomatic edema.
4. Endocrinopathies.
   a. Hydrocortisone (adrenal insufficiency).
   b. Levothyroxine (hypothyroidism).
   c. Desmopressin (DDAVP) for DI:
      i. IV or subcutaneous: 2 to 4 µg/day in two divided doses.
      ii. Intranasal (100 µg/mL solution): 10 to 40 µg/day divided one to three times per day.
      iii. Fluid restriction.
5. Hyponatremia.
   a. Fluid restriction for SIADH or fluid replacement for CSW.
   b. Three percent hypertonic saline or 23.4% NaCl if symptomatic.
   c. Do not correct >12 mEq/day due to risk of central pontine myelinolysis.
6. Central nervous system infection.
   a. Antibiotics.
   b. Drain infections, remove infected bone flap.

VI. SPINAL TUMORS

A. Background: ICU care indicated if there are postoperative ventilator issues.

B. Pathophysiology/etiology.

1. Tumor compression.
2. Spinal cord ischemia and infarction.
3. Postoperative hemorrhage.
4. Autonomic dysfunction.

C. Diagnosis.

1. **Clinical presentation.**
   a. Respiratory insufficiency.
      i. Paralysis of intercostal muscles (lesions C6 and below).
      ii. Decreased diaphragmatic and accessory respiratory muscle function (lesions above C6).
   b. Other.
      i. Ileus.
      ii. Urinary retention.
      iii. Hypotension.
      iv. Bradycardia.
2. **Radiologic studies.** MRI more specific than CT.
3. **Tests/laboratory studies.**
   a. Oxygen saturation with vital capacities every 6 hours.
   b. Frequent neurologic exams.

D. Treatment.

1. Indications for mechanical ventilation:
   a. Vital capacity < 10 to 15 mL/kg.
   b. Hypoxia (Spo_2 < 90%, Pao_2 < 55).
   c. Inability to ventilate (rising $PaCo_2$, respiratory acidosis, mental status change), patient unable to protect airway.
2. Ileus: nasogastric or orogastric tube.
3. Urinary retention: urinary catheter.
4. Vasopressors to maintain systolic blood pressure >90 mm Hg.
5. Atropine versus pacing for symptomatic bradycardia.
6. Surgery to relieve cord compression.
7. Orthosis (bracing) may provide support during healing.
8. Radiation therapy:
   a. May be primary treatment of metastatic disease.
   b. Also for residual postoperative disease.

VII. SYSTEMIC COMPLICATIONS SECONDARY TO BRAIN TUMORS

A. Pathophysiology.

1. Immobility.
2. Hypercoagulable state.
3. Local or systemic infection.

B. Diagnosis.

1. **Clinical manifestations.**
   a. Deep venous thrombosis (DVT).
   b. Pulmonary embolus.
   c. Systemic infection.
   d. Urinary tract infection.
   e. Pneumonia.
   f. Line sepsis.
   g. Meningitis.
2. **Radiologic studies.**
   a. Chest radiograph for pneumonia.
   b. Venous duplex scan for deep vein thrombosis.
   c. Pulmonary embolus.
      i. CT pulmonary embolus protocol.
      ii. Ventilation perfusion scan.
3. **Laboratory studies.**
   a. Complete blood count.
   b. Complete metabolic profile.
   c. Urinalysis and culture.
   d. Sputum Gram stain and culture.
   e. Central line tip culture.
   f. Blood cultures.
   g. Lumbar puncture for CSF analysis.

C. Treatment.

1. Antibiotics.
2. DVT prophylaxis.
   a. Thromboembolic deterrent (T.E.D.) hose.
   b. Leg sequential compression devices (SCDs).
   c. Pharmacologic subcutaneous therapy (if no evidence of active bleeding).
      i. Low-dose unfractionated heparin 5,000 units two to three times per day.
      ii. Enoxaparin 30 mg twice daily or 40 mg daily.
   d. Warfarin (Coumadin) is generally safe if patient is >2 weeks postoperative and is not actively bleeding.

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129 Miscellaneous Intensive Care Unit Neurologic Problems

David Cachia, Nancy M. Fontneau, and Ann L. Mitchell

I. OVERVIEW

A variety of disorders affecting the nervous system, not easily categorized otherwise, require management in the intensive care unit (ICU). These include the following:

- **A.** Suicidal hanging.
- **B.** Electrical injuries.
- **C.** Carbon monoxide (CO) poisoning.
- **D.** Decompression syndrome ("the bends").
- **E.** Cerebral fat embolism.
- **F.** Hiccups.
- **G.** Peripheral nerve disorders.

II. SUICIDAL HANGING

Second most common means of committing suicide among adolescents in the United States (US).

A. Pathophysiology.

1. Death is usually by slow strangulation with compression of the jugular veins or carotid arteries.
2. Interruption of blood flow for more than a few minutes results in hypoxic–ischemic injury with neuronal death, cytotoxic/vasogenic edema, and increased intracranial pressure (ICP).

B. Prognosis.

1. Poor prognostic signs.
   - **a.** Evidence of cardiopulmonary arrest, low Glasgow Coma Scale score.
   - **b.** Spontaneous respiratory rate of <4/minute, need for intubation.
   - **c.** Neurogenic pulmonary edema.

C. Management.

1. Cardiopulmonary resuscitation and treatment for cardiac arrhythmias.
2. Monitor for paratracheal/laryngeal trauma, or acute respiratory distress syndrome; endotracheal intubation can prevent airway obstruction.
3. Cervical spine should be stabilized until fracture is excluded or treated.
4. Treatment of increased ICP.
5. A carotid thrombus requires prompt vascular intervention.

III. ELECTRICAL INJURIES

In the US, there are 4,000 injuries and 1,000 deaths from electric shock annually.

A. Pathophysiology.

1. Immediate effects.
   - **a.** Ten to fifty percent experience transient unconsciousness, headaches, or retrograde amnesia.
   - **b.** Brain hemorrhages occur with electrical injuries to the head. Spinal cord injuries are more common when electricity spreads from the ground to the patient.
   - **c.** Catecholamine release may result in autonomic dysfunction: diaphoresis, fixed dilated pupils, and keraunoparalysis (reversible limb paralysis accompanied by vasospastic vascular compromise following lightning injury).
2. Delayed effects.
   - **a.** Neuropsychiatric effects—for example, depression, memory impairment.
   - **b.** Reflex sympathetic dystrophy.
   - **c.** Myelopathies/motor neuronopathy.

B. Prognosis.

1. Difficult to ascertain initially, since patients with deficits at presentation may recover fully, while those with delayed onset of neurologic deficits may have syndromes that linger for months.

C. Management.

1. Specific treatment for neurologic injuries secondary to electrical injuries not available.
2. Supportive medical/surgical care.

IV. CARBON MONOXIDE POISONING

In physiologic amounts, endogenous CO functions as a neurotransmitter. Atmospheric CO concentration is normally <0.001%; concentrations of 0.1% can be fatal.

A. Pathophysiology.

1. CO's affinity for hemoglobin is more than 200 times that of oxygen, resulting in the formation of carboxyhemoglobin with even relatively low amounts of inhaled CO.
2. Clinical effects depend on the carboxyhemoglobin level and duration of exposure.
   - **a.** Mild exposures result in headache, myalgia, dizziness, or neuropsychological impairment.
   - **b.** Severe exposures to CO result in confusion, loss of consciousness, or death.

B. Treatment.

1. One hundred percent oxygen by a tight-fitting nonrebreathing face mask.
2. One hundred percent oxygen shortens half-life of CO from 4 to 5 hours to approximately 1 hour.
3. Hyperbaric oxygen therapy may be useful but remains controversial.

C. Prognosis.

1. Approximately 75% recover within a year of the insult.
2. Approximately 10% to 30% develop memory impairment or extrapyramidal signs reminiscent of parkinsonism. Basal ganglia and substantia nigra neurons are highly sensitive to CO exposure.

V. DECOMPRESSION SICKNESS ("THE BENDS")

A. Decompression sickness can arise in the following cases:

1. Rapid ascent of scuba divers or tunnel workers.
2. Decompression of high-altitude flying aircraft with inadequate cabin pressure.
3. Flying *too soon* after scuba diving (sooner than 18 to 24 hours).

B. Pathophysiology.

1. Decompression sickness occurs when gases dissolved in body fluids under high atmospheric pressure come out of solution under conditions of lower pressure. Small gas bubbles form, causing local tissue ischemia or venous obstruction.
2. Neurologic symptoms are seen in approximately 80% of patients.
   a. Focal or diffuse paresthesias are the most frequent symptoms, affecting the skin and joints.
   b. Weakness of one or more limbs, secondary to spinal cord involvement.
   c. Cerebral symptoms are less frequent and include visual disturbances, vertigo, headache, lethargy, or unconsciousness.
3. Air embolism is a severe and acute complication of decompression illness.
   a. Onset is usually within 5 minutes of decompression.
   b. Overinflation of the lungs causes rupture of lung parenchyma and gas bubble formation in the pulmonary veins.
   c. Cerebral arterial embolism can occur in patients with a patent foramen ovale.
      i. Unconsciousness and stupor are the most common symptoms.
      ii. Cardiopulmonary arrest can occur.

C. Treatment.

1. Recompression in a hyperbaric chamber is the definitive treatment.
   a. Begin recompression as quickly as possible. Results are best when recompression is done within 12 hours of symptom onset in decompression sickness and within 4 hours of symptom onset in air embolism.
   b. Recompression should be attempted up to 2 weeks after onset of symptoms.
2. Interim management—supportive care: Administer 100% oxygen (with air breaks to avoid pulmonary oxygen toxicity), intubate if pulmonary edema develops, provide circulatory support with colloid, and use vasopressors if required.
3. Emergency phone numbers: The Divers Alert Network consultation service (*www.diversalertnetwork.org*): (919) 684-9111.

D. Prognosis.

1. Most patients improve when the gas bubbles redistribute to the venous circulation.
2. Remarkable recovery can occur after recompression.
   a. Relapse requiring repeated decompression treatment occurs in 30% to 50% of patients.

VI. CEREBRAL FAT EMBOLISM SYNDROME

A. Pathophysiology.

1. Consequence of long bone fracture, particularly lower limb fractures.
   a. Present in up to 2% of patients with long bone fractures, 5% to 10% of multitrauma patients.
   b. Presents 12 to 48 hours after trauma.
2. Symptoms depend on the location of fat emboli.
   a. Hypoxemia from pulmonary insufficiency.
   b. Neurologic.
      i. Confusion, impaired consciousness, or coma.
      ii. Seizures.
      iii. Focal neurologic signs are present in approximately one-third of patients.
   c. Other signs and symptoms: Fever, tachycardia, cutaneous petechiae, thrombocytopenia, and anemia.
   d. MRI brain: T1 hypointensities and T2 hyperintensities. Diffusion-weighted images may also display lesions.
3. Pathology.
   a. Microscopic fat emboli in the gray matter.
   b. Perivascular hemorrhages predominantly in the cerebral and cerebellar white matter.
   c. Cerebral edema.

B. Management.

1. Rapid immobilization and early definitive management of fractures.
2. Monitor and correct oxygenation; provide adequate fluid resuscitation.
3. Imaging of the brain to rule out direct traumatic brain injury as the cause of neurologic symptoms.

C. Prognosis.

1. Mortality rate: <10%.
2. Permanent neurologic deficit: 25% of patients.

VII. HICCUPS (SINGULTUS)

A. Background.

1. Hiccups are usually a benign, self-limited condition.
2. Prolonged hiccupping can produce fatigue, sleeplessness, weight loss, difficulty in ventilation.

B. Pathophysiology.

1. Troublesome hiccupping is most commonly associated with chest, abdomen, neck, and brainstem disorders.
2. Lateral medulla, phrenic nerve, or vagus nerve injuries are usual causes.
3. Other causes: metabolic disorders (e.g., uremia), pacemaker malfunction, toxins, reflux disease, certain medications, for example, α-methyldopa, corticosteroids, benzodiazepines, and opioids.

C. Management.

1. Find and treat underlying structural or metabolic disorder.
2. Medication options.
   a. Chlorpromazine (25 to 50 mg) by mouth or intramuscularly (IM) up to three/four times a day.
   b. Intravenous infusion of chlorpromazine (25 to 50 mg in 500 mL of normal saline) if oral or IM is ineffective. However, chlorpromazine has many potentially serious side effects.
   c. Metoclopramide (10 mg) orally four times a day.
   d. Haloperidol (5 mg) three times a day may also prove effective.
   e. Gabapentin (100 to 400 mg) three times a day.
   f. Baclofen: from 5 mg twice daily to 20 mg three times daily.
3. Mechanical treatments for hiccups alter the responsible reflex arc by direct stimulation of the posterior pharynx (tickling) by nasogastric tube.
4. Refractory hiccups.
   a. Vagus nerve stimulation.
   b. Transcutaneous stimulation of the phrenic nerve/phrenic nerve block.

VIII. PERIPHERAL NERVE DISORDERS

A. Critical illness polyneuropathy (see Chapter 127).

B. Compression neuropathies developing in the ICU.

1. Can result in significant delayed morbidity.
2. Clinical features: Compression of the peroneal nerve at the fibular head and the ulnar nerve at the elbow are the most common, with weakness and numbness in nerve distributions.
3. Prevention: Avoid compression by proper patient positioning.
4. Treatment: Supportive in most patients.

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130 CNS Infectious and Inflammatory Disorders

Neeta Garg and Peter N. Riskind

I. CLASSIFICATION

A. *Infectious.*

1. Encephalitis.
- **a.** Viral (see section I.A.2.b.i. below).
- **b.** Nonviral.
  - **i.** Bacterial—Tuberculosis, *Mycoplasma pneumoniae*, *Listeria monocytogenes*, *Borrelia burgdorferi*, *Bartonella henselae*, *Leptospira*, *Brucella*, *Salmonella typhi*, *Treponema pallidum.*
  - **ii.** Rickettsial disease.
  - **iii.** Fungal—cryptococcal, coccidioidomycosis, histoplasmosis, candidiasis.
  - **iv.** Parasitic infections—African trypanosomiasis, *Toxoplasmosis gondii*, Schistosomiasis, *Echinococcus.*

2. Meningitis.
- **a.** Bacterial.
  - **i.** Newborn: Group B *Streptococcus*, *Escherichia coli*, *L. monocytogenes.*
  - **ii.** Childhood: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b.
  - **iii.** Adults: *Neisseria meningitidis*, *Streptococcus pneumoniae.*
- **b.** Nonbacterial.
  - **i.** Viral (herpes simplex virus 1 [HSV1] , HSV 2, enteroviruses, varicella zoster (VZV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), lymphocytic choriomeningitis, rubella, rubeola, mumps, St. Louis encephalitis, West Nile virus).
  - **ii.** Fungal, parasitic, rickettsial as above.
  - **iii.** Parasitic (*Naegleria fowleri*).

B. Noninfectious or autoimmune.

1. Acute disseminated encephalomyelitis (ADEM).
2. Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis (Table 130-1).
3. Transverse myelitis (TM).
- **a.** Idiopathic transverse myelitis (ITM).
- **b.** Secondary TM (associated with infections, vasculitis, sarcoidosis).
  - **i.** Neuromyelitis optica (NMO) or Devic disease.
  - **ii.** Multiple sclerosis.

TABLE 130-1 Clinical Features of Anti-NMDA Encephalitis and Idiopathic Transverse Myelitis

	Definition	Pathogenesis	Clinical manifestation	Diagnostic workup	Treatment
Anti-NMDA encephalitis	A rare encephalitis syndrome seen in patients with teratomas and small cell lung cancer; 40% cases not seen with tumor Associated with antibodies against NR1 and NR2 heteromers of the NMDA receptor	Probably caused by immune-mediated response due to cross-reactivity between native NMDA receptors and tumor cells expressing NMDA receptors	Commonly seen in young women; presents with psychiatric, cognitive, and autonomic symptoms followed by seizures, dyskinesias, and ataxia, and encephalopathy May be preceded by viral like syndrome	Clinical history Brain MRI may be normal or show nonspecific increase in T2 or FLAIR signal in the temporal lobes, brainstem, basal ganglia, and cerebral cortex CSF may show pleocytosis, oligoclonal bands, and NR1 antibodies	Variable response to empirical treatment with corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange (PE). Recovery usually slow, persistent amnesia common Rituximab (anti-CD 20 monoclonal antibody) may be considered
ITM	Severe focal inflammatory disorder of spinal cord resulting in devastating myelopathy syndrome	Believed to be postinfectious autoimmune process, as often follows an antecedent infection	Acute or subacute myelopathic syndrome with motor, sensory, and autonomic involvement; respiratory involvement may be seen with high cervical lesions	Rapidly progressive severe myelopathy MRI—mono or multifocal cord lesions, may show enhancement; the length of lesions varies from one to many CSF—pleocytosis, elevated protein, variable oligoclonal band positivity	Prognosis variable; most patients left with moderate-to-severe disability

iii. Central nervous system (CNS) vasculitis.
iv. Sarcoidosis and other inflammatory disorders.

II. ENCEPHALITIS

A. Definition: Inflammation of brain parenchyma associated with clinical evidence of brain dysfunction, in most cases associated with inflammatory meningeal involvement as well, hence the term meningoencephalitis.

B. Epidemiology.

1. Incidence of encephalitis among adults in the US is 2.0 to 2.5 cases per 100,000 persons per year.
2. Causative agents.
   a. Most encephalitis cases are of viral etiology.

C. Prognosis.

1. Mortality and morbidity depend on the specific pathogen and immunologic status of the patient.
2. With HSV, mortality reaches up to 50% to 70% without treatment, but is high even with treatment; Japanese encephalitis also has high mortality.
3. Overall mortality is 50%, lower with eastern equine encephalitis (EEE) and St. Louis encephalitis.
4. Tends to be more severe among very young and very old.

D. Etiology.

The following viruses are implicated in causing encephalitis, with the most common agents indicated by asterisk:

1. HSV type 1* and 2 (usually causes aseptic meningitis).
2. Varicella zoster virus*.
3. Epstein-Barr virus (EBV)*.
4. Enterovirus*.
5. Measles*.
6. Mumps*.
7. Arbovirus (Eastern equine and Western equine, St. Louis, West Nile, Dengue, Japanese B encephalitis).
8. Others: Poliovirus, influenza, lymphocytic choriomeningitis, rabies, CMV (seen in patients with HIV), progressive multifocal leukoencephalopathy (PML) (seen in immunocompromised patients), HIV.

E. Pathogenesis.

1. Viral entry via bloodstream, except after head trauma or neurosurgery.
2. Innate immune responses to infectious components cause leukocyte infiltration, altered cerebral blood flow.
3. Symptoms and signs are related to meningeal irritation.
4. Altered neurologic function is due to metabolic and circulatory disturbances.

F. Diagnosis.

1. History.
   a. The diagnosis should be suspected in a febrile patient with altered mental status.

b. Other neurologic findings: seizures, focal neurologic disturbances (e.g., aphasia, hemiparesis, hemianopsia), neuropsychiatric symptoms such as psychosis, agitation, personality and behavioral changes, and cognitive dysfunction.

c. History of travel, contact with animals and sick persons, insect bite, immune status, and occupational history may be important.

2. Physical exam.

a. General exam.

i. May provide clues to etiology. Skin rash, parotitis (mumps), signs of upper respiratory infection, cardiomyopathy.

ii. Other findings may indicate complications—autonomic dysfunction, diabetes insipidus, or syndrome of inappropriate antidiuretic hormone secretion (SIADH).

b. Neurologic exam.

i. Diffuse and focal cerebral dysfunction—altered consciousness may range from lethargy to coma; reflects the severity of encephalitis; focal neurologic deficits may be present.

ii. Meningismus—due to associated meningitis.

3. Laboratory studies.

a. Blood.

i. Blood count—lymphocytosis commonly seen.

ii. Blood culture, chest x-ray—general workup for febrile illness.

iii. Virologic studies—antibodies to common viruses, including HSV-1 and 2, VZV, HV-6 and 7, CMV, EBV, HIV, influenza A and B, and some enteroviruses: measured in the serum, and ratio in serum and cerebrospinal fluid (CSF) can be measured for intrathecal antibody production.

b. CSF analysis—an essential part of the diagnostic workup; should be performed promptly except when there is a suggestion of a mass lesion.

i. Mild lymphocytic pleocytosis, <50 cell/mm^3, mildly elevated protein, and normal glucose in most cases (similar to aseptic meningitis).

ii. A higher lymphocytic count or neutrophilic predominance may indicate alternative diagnoses such as tuberculous or bacterial meningitis or acute hemorrhagic leukoencephalitis.

iii. Immunocompromised patients may not show CSF lymphocytosis due to failure to mount an inflammatory response.

iv. Hemorrhagic fluid (with nontraumatic tap) can be seen in herpes simplex encephalitis (HSE) and acute hemorrhagic leukoencephalitis (AHLE).

v. Low CSF glucose is unusual in viral encephalitis, and may indicate bacterial, fungal, or parasitic meningoencephalitis.

vi. CSF antibodies to virus and specific viral culture are usually not helpful, as the results take a few days; treatment is often initiated before available.

vii. Polymerase chain reaction (PCR) for viral DNA amplification can be performed rapidly (within 6 to 8 hours) and is highly

specific and sensitive (>95%) if obtained within the first week of onset of symptoms, requires only small amount of CSF, and is available for HSV-1 and 2, VZV, human herpes virus (HHV)-6 and 7, CMV, EBV, HIV, and enteroviruses viruses.

c. Virus detection from other body sources such as blood, urine, stool, and throat secretions are less specific.

d. Neuroimaging/radiologic studies.

i. Cranial computed tomography (CT)—initial screening prior to magnetic resonance imaging (MRI).

ii. MRI of the brain.

(a) More sensitive than CT scan—leptomeningeal enhancement may be present.

(b) May show edema, mass effect, hemorrhage, and contrast enhancement in temporal lobes and insula in HSV encephalitis.

(c) Initial changes may include high signal intensity on T2-weighted image (T2WI) and fluid attenuated inversion recovery (FLAIR) secondary to edema.

(d) Involvement of the cingulate gyrus and bilateral temporal lobes is typical of HSV encephalitis.

(e) Ischemic or hemorrhagic infarctions—can be seen with VZV encephalovasculitis.

(f) Basal ganglia and thalamic involvement—Japanese and EBV encephalitis.

d. EEG.

i. Diffuse slowing of background rhythm in most cases.

ii. In HSE, focal slowing or periodic lateralized epileptiform discharges (PLEDS) in bilateral temporal lobes.

G. Treatment. Suspected cases of viral encephalitis should be treated urgently.

1. Acyclovir should be started empirically as soon as possible while waiting for CSF results, using dose of 10 mg/kg every 8 hours intravenously for 10 days. Drug dosing should be adjusted in patients with renal impairment.

2. Vidarabine 15 mg/kg/d is an alternative, less effective than acyclovir when used for HSV and VZV encephalitis.

a. Acyclovir and vidarabine are of no benefit in nonherpetic encephalitis cases.

3. Corticosteroids.

a. Limited role in patients with VZV encephalitis complicated by vasculitis.

b. Occasionally also used for severe HSE with severe cerebral edema.

4. Supportive care.

a. Seizure management with antiepileptic medications.

III. ACUTE DISSEMINATED ENCEPHALOMYELITIS

A. Definition.

A fulminant monophasic CNS autoimmune syndrome with inflammation and demyelination, typically following immunization (postvaccination, encephalomyelitis) or infection (postinfectious demyelination).

B. Epidemiology.

1. More common in the younger population; may be related to high rate of infection and vaccination in this group.
2. Slight male predominance in the pediatric population; more prevalent in spring and winter.
3. About 10% to 15% cases of acute encephalitis in the United States; overall incidence is 0.4 per 100,000 per year; incidence in adults unknown.

C. Etiology.

1. Believed related to preceding infection/immunization triggering a cell-mediated and humoral autoimmune response resulting in inflammation and demyelination.
2. Measles virus, the most common antecedent infection prior to measles vaccine. Seen with mumps, rubella, VZV, EBV, CMV, HSV, coxsackie viruses as well.
3. Bacterial and parasitic infections—*Mycoplasma pneumoniae*, *Streptococcus*, malaria, *Borrelia burgdorferi*—are less frequently implicated.
4. Among vaccines, Semple Rabies and earlier strains of smallpox vaccine have the strongest correlation.

D. Pathogenesis.

1. Possible "molecular mimicry and self sensitization"—induction of autoantibodies and/or T cells by epitopes of a virus, vaccine, or other antigens cross-reactive to the epitopes on CNS myelin or axonal glycoprotein.
2. Inflammatory response causes demyelination by activated macrophages, and oligodendrocyte damage by cross-reacting antibodies and complement fixation.
3. Pathologically—perivenular infiltrates of T cells and macrophages with associated perivenular demyelination. AHLE is a variant with inflammatory damage to blood vessels.

E. Clinical presentation.

1. Monophasic rapidly progressive encephalopathy syndrome (usually in young children or adults) with headache and altered sensorium (confusion, stupor, or coma), with or without meningismus and focal neurologic deficits and seizures.
2. Prodromal history of vaccination or infection days to weeks previously.
3. Focal neurologic deficits may include hemiparesis, hemianopsia, cranial nerve deficits, ataxia, and myelopathy.
4. Absence of fever or mild fever at the onset.
5. In children with chickenpox—typical acute ataxia syndrome seen secondary to postinfectious meningocerebellitis.
6. AHLE—more rapidly progressive, fulminant course; mortality is high.

F. Laboratory studies.

1. Routine blood studies.
   a. May show mild leukocytosis.
   b. Serologic studies for preceding infection are often negative.

2. CSF—changes are usually nonspecific.
   a. Mild lymphocystic pleocytosis, <50 cell/mm^3, mildly elevated protein, and normal glucose in most cases.
   b. Oligoclonal bands usually absent.
   c. MRI—mainstay of diagnosis in the last decade.
      i. Classic findings include multifocal or diffuse subcortical lesions with high signal intensity on T2WI and FLAIR; can be asymmetric.
      ii. Basal ganglia and thalamic involvement may be seen.

G. Prognosis.

1. Usually good with gradual recovery over weeks to months in majority of cases.
2. Some patients may be left with residual neurologic deficits.
3. AHLE has a less favorable outcome.

H. Treatment.

1. No standardized treatment protocol; immunomodulatory drugs are the mainstay of treatment.
2. High-dose corticosteroids—500 to 1,000 mg (20 to 30 mg/kg) methylprednisolone IV daily for 3 to 7 days or dexamethasone 100 to 200 mg (1 to 3 mg/kg) daily for 5 days; follow-up oral prednisone taper.
3. Intravenous immunoglobulin (1 to 2 g/kg given over 5 days) or plasma exchange is used in cases of steroid failure.

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SECTION 14

Transplantation

Sonia N. Chimienti and Christoph Troppmann

131 Critical Care of Organ Transplant Recipients: Overview

Christoph Troppmann

I. GENERAL PRINCIPLES

A. The increased number of organ transplants (28,051 transplants in the United States in 2012, compared with 12,623 in 1988) has been paralleled by significant improvements in both patient and graft survival. These improvements can be attributed to several factors.

1. The availability of polyclonal and monoclonal antibody preparations (antithymocyte globulin, anti-CD 52–directed alemtuzumab, and anti-IL-2 receptor–directed basiliximab) to prevent and treat rejection episodes.
2. The introduction in the 1980s of a powerful immunosuppressant agent, cyclosporine, followed a decade later by tacrolimus and mycophenolate mofetil. More recently, additional new drugs have become available (e.g., sirolimus, everolimus, belatacept), augmenting the immunosuppressive armamentarium considerably and allowing for more individualized immunosuppression of organ recipients.
3. Improvements in organ preservation (e.g., introduction of the University of Wisconsin preservation solution in the late 1980s).
4. Thorough preoperative patient screening.
5. Increasing sophistication in postoperative intensive care, allowing also for transplantation in high-risk recipients with significant medical comorbidities.

6. Availability of potent, yet nontoxic antibacterial, antifungal, and antiviral agents has allowed for more effective prevention and treatment of opportunistic infections.
7. Refinements in surgical techniques.

B. Transplantation has therefore become the treatment of choice for many patients with end-stage failure of kidneys, liver, endocrine pancreas, heart, lungs, and small bowel. Criteria for potential recipients have been expanded to include infants, children, and individuals thought to be at higher risk for complications (e.g., patients with diabetes, elderly patients).

C. Current absolute contraindications to transplantation include malignancy (untreated, metastatic, or at high risk for recurrence); uncontrolled infection; and medical–surgical contraindications to undergo, or inability to recover from, a major surgery.

D. The gap between available organs and patients awaiting transplantation is widening. As a result, mortality on many transplant wait lists is increasing.

II. THE ORGAN DONOR SHORTAGE: POTENTIAL SOLUTIONS

A. Live donors.

1. Owing to the lack of deceased organ donors, and the development of a noninvasive (laparoscopic) nephrectomy technique, the number of live donor kidney transplantation has significantly increased. In 2001, for the first time, live kidney donors outnumbered deceased kidney donors in the United States. Current initiatives (e.g., wider implementation of paired kidney exchange for incompatible live donor–recipient pairs) aim at increasing live donor transplant rates even further.
2. Live donor liver, small bowel, and lung transplants are also performed but continue to represent only a very small proportion (<4%) of each of those transplants.

B. Deceased organ donors.

1. The overall number of deceased organ donors in the United States has increased by 36% over the past decade (5,985 donors in 2000 vs. 8,143 donors in 2012).
2. Brain dead donors: still by far the most common deceased donor type (88.3% of all deceased donors in the United States in 2011).
3. Donation after cardiac death (DCD) donors: an increasingly used donor type. In a typical scenario, families of unconscious patients who do not fulfill the formal criteria of brain death (e.g., patients with severe, irreversible terminal brain injury or neurological disorders), decide to forego any further treatment and then decide to donate the organs. In 2011, DCD donors represented 11.7% of all deceased organ donors in the United States.
4. Maximizing donation within the currently underused pool of potential brain dead and DCD donors carries the most significant potential for substantially increasing the number of available organs for transplantation. Critical care physicians and other intensive care health personnel play a crucial role in optimizing the rate of conversion from being a potential donor to being an actual donor (see also Chapter 132).

C. Unconventional donor organ sources (e.g., liver or heart domino transplants, reuse of already transplanted organs) cannot *significantly* increase the number of available organs. Paying live organ donors is against federal law in the United States and is currently not an option in Western industrialized countries.

III. ORGAN-SPECIFIC CONSIDERATIONS

A. Kidney transplantation.

1. Treatment of choice for nearly all patients of all ages with advanced chronic kidney disease (CKD).
2. Kidney transplants do not only improve quality of life but also prolong life.
3. Less expensive from a socioeconomic standpoint than chronic hemodialysis.

B. Liver transplantation.

1. Treatment of choice for most patients with acute and chronic end-stage liver disease.
2. Dramatic improvement in graft survival after introduction of cyclosporine in the early 1980s. Currently, no reliable means exists to substitute for a failing liver other than with a transplant.
3. Attempts to alleviate the severe donor shortage include the increased use of nonstandard criteria donors and innovative surgical techniques (e.g., living donor and split-liver transplants).

C. Pancreas and islet transplantation.

1. Indications: most pancreas and islet transplants are done for selected, medically suitable patients with type 1 diabetes who have developed significant secondary diabetic complications or have poor quality of life (e.g., due to severe hypoglycemic unawareness).
2. At present, pancreas transplantation is the only effective option to consistently restore normal glucose homeostasis and normalize glycosylated hemoglobin (HbA1c) levels.
3. Successful pancreas transplants significantly improve quality of life and decrease incidence and severity of secondary diabetic complications.
4. Most pancreas transplants are performed simultaneously with a kidney transplant in patients with advanced CKD due to diabetic nephropathy.

D. Small bowel transplantation.

1. Indications: congenital or acquired short bowel syndrome, especially if liver dysfunction occurs because of long-term parenteral nutrition or if establishing or maintaining central venous access becomes difficult.
2. In patients who also have advanced liver disease, a combined liver–small bowel transplant may be indicated.
3. With refinement of surgical techniques, more specific immunosuppression, and better postoperative monitoring for rejection, graft survival has considerably improved and now approaches that of other solid organ grafts (e.g., lung transplants).

E. Heart transplantation.

1. Treatment of choice for patients with end-stage congenital and acquired parenchymal and vascular diseases of the heart after exhaustion of all conventional medical and surgical options.
2. Results have considerably improved since the introduction of cyclosporine in the early 1980s and after refinements in diagnosing and treating rejection episodes.
3. Mechanical devices (e.g., ventricular-assist devices) can serve as a temporary bridge to heart transplantation.

F. Heart–lung and lung transplantation.

1. Effective treatment for patients with advanced pulmonary parenchymal or vascular disease with or without primary or secondary cardiac involvement.
2. Increase in lung transplants (most frequently done as single or bilateral single lung transplants) is in large part due to technical improvements, resulting in fewer surgical complications, and to advances in perioperative and postoperative care.
3. Mechanical ventilation or extracorporeal membrane oxygenation (ECMO) can be a temporary bridge to transplant.

G. Hematopoietic cell transplantation—see Chapter 138.

IV. FUTURE CHALLENGES IN ORGAN TRANSPLANTATION

A. Increase number of available donor organs.
B. Minimize rates of chronic graft failure (e.g., secondary to chronic rejection).
C. Develop immunosuppressive drugs and protocols that have fewer side effects and further improve long-term graft survival.
D. Develop tolerance-promoting protocols that would obviate the need for chronic immunosuppression beyond the induction phase.
E. Develop clinically useful transplantation biomarkers to individualize the care of transplant recipients and to minimize the incidence and effects of acute and chronic allograft rejection.

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132 Critical Care of the Deceased Organ Donor

Christoph Troppmann

I. GENERAL PRINCIPLES

A. The gap between available donor organs and those waiting for transplants is widening, and the wait list mortality has been increasing.

B. Critical care physicians and other health care personnel play a key role in (1) early identification of potential organ donors; (2) early referral to organ procurement organizations (OPOs); (3) a coordinated approach to the potential donors' families for obtaining consent; and (4) maintaining and optimizing organ function and viability for transplantation. Physicians providing end-of-life care should routinely consider the option of organ donation (see also Chapter 23).

C. Predicted annual number of brain-dead potential organ donors in the United States ranges between 10,500 and 13,800, but in 2012, organs were recovered from only 8,143 deceased donors.

II. DONOR CLASSIFICATION

A. Brain-dead deceased donors.

1. The most common deceased donor type (88.3% of all deceased donors in the United States in 2011).

2. Unequivocal diagnosis of brain death is required before proceeding with organ recovery.

B. Donation after cardiac death (DCD) donors.

1. DCD donors have been increasing substantially in the United States over the past decade and currently represent 11.7% of all deceased organ donors.

2. Usually, time and place of death are controlled (e.g., families of patients with severe irreversible terminal brain injuries, refractory medical diseases, or advanced neurologic disorders, who do not fulfill the formal criteria of brain death, decide to withdraw all life-sustaining technology and then decide to donate the organs).

3. Supportive treatment is withdrawn in the ICU or the operating room, and organ recovery is initiated once death has been pronounced by a physician not belonging to the organ recovery and transplant team.

III. PATIENT SCREENING (FOR POTENTIAL BRAIN-DEAD DECEASED DONORS AND DONATION AFTER CARDIAC DEATH DONORS)

A. Age 0 to 90 years.

B. Severe neurologic injury (trauma, cerebrovascular accident [CVA], hypoxia, brain tumor), or near brain death, or brain-dead (with or without impending withdrawal of support), or intent to withdraw support in non–brain-dead patients with other terminal nontraumatic conditions (e.g., advanced neurological disease).

C. Patients with systemic bacterial or fungal infections, and those with localized viral infections, may in some cases still be considered as organ donors. Intensive care physicians caring for potential donors with these criteria should consult with the local OPO, where the ultimate decision regarding organ donor candidacy is made, together with the Transplant Center.

D. Absolute contraindications.

1. Viral encephalitis with systemic viral infection.
2. Human immunodeficiency virus (HIV) positive.
3. Malignancy (except nonmelanoma skin cancers and primary brain tumors with little propensity to disseminate).

E. After identification of any potential donor, federal required request legislation mandates that hospitals notify their local OPO in a timely manner.

F. If the local OPO address is unknown, a 24-hour access number to the United Network for Organ Sharing (UNOS) is available for further referral information: 1-800-292-9537.

G. The OPO will assist with completing preliminary screening of the potential donor and coordinating the approach to the potential donor's family and will consult with the transplant team(s) regarding use of donor organs that do not meet standard criteria.

IV. BRAIN DEATH DIAGNOSIS

A. "An individual who has sustained either irreversible cessation of circulatory and respiratory function or irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted standards" (President's Commission for the Study of Ethical Problems in Medicine *Uniform Determination of Death Act*, 1981).

B. The clinical diagnosis of brain death rests on three criteria:

1. Irreversibility of the neurologic insult.
2. Absence of clinical evidence of cerebral function.
3. Most important, absence of clinical evidence of brainstem function.

C. Clinical brain death examination and apnea test are outlined in Table 132-1.

D. Spinal reflexes can be preserved and do not exclude the diagnosis of brain death.

V. OBTAINING CONSENT FOR ORGAN DONATION

A. Early involvement of the OPO in the potential organ donor screening and organ donation and consent process is crucial.

TABLE 132-1 Brain Death Criteria and Clinical Diagnosis of Brain Death

1. Irreversible, well-defined etiology of unconsciousness:
   a. Structural disease or metabolic cause (hypoxia).
   b. Exclusion of hypothermia; hypotension; severe electrolyte, glycemic, uremic, endocrine, or acid–base disturbance; hepatic encephalopathy; drug or substance intoxication.
   c. Sufficient observation period (at least 6 h) between two brain death examinations.
2. No clinical evidence of cerebral function:
   a. No spontaneous movement, eye opening, or movement or response after auditory, verbal, or visual commands.
   b. No movement elicited by painful stimuli to the face and trunk (e.g., sternal rub, pinching of a nipple or fingernail bed) other than spinal cord reflex movements.
3. No clinical evidence of brainstem function:
   a. No pupillary reflex: pupils are fixed and midposition; no change of pupil size in either eye after shining a strong light source in each eye sequentially in a dark room.
   b. No corneal reflex: no eyelid movements after touching the cornea (not the conjunctiva) with a sterile cotton swab or tissue.
   c. No gag reflex: no retching or movement of the uvula after touching the back of the pharynx with a tongue depressor or after moving the endotracheal tube.
   d. No cough reflex: no coughing with deep tracheal irrigation and suctioning.
   e. No oculocephalic reflex (doll's eyes reflex): no eye movement in response to brisk turning of the head from side to side with the head of the supine patient elevated 30°.
   f. No oculovestibular reflex (caloric reflex): no eye movements within 3 min after removing earwax and irrigating each tympanic membrane (if intact) sequentially with 50 mL ice water for 30–45 s while the head of the supine patient is elevated 30°.
   g. No integrated motor response to pain: no localizing or withdrawal response, no extensor or flexor posturing.
4. Apnea testing:
   a. Patient must be normothermic (>36.5°C) and normotensive (systolic blood pressure >90 mm Hg).
   b. Patient is preoxygenated with FiO_2 of 1.0 for 10–15 min while adjusting ventilatory rate and volume so that $paCO_2$ reaches 40–45 mm Hg.
   c. Obtain arterial baseline blood gas, disconnect the patient from the ventilator, deliver O_2 at 6–8 L/min through a cannula advanced 20–30 cm into the endotracheal tube (cannula tip at the carina).
   d. Use continuous pulse oximetry for early detection of desaturation.
   e. If brain-dead, a $paCO_2$ >60 mm Hg is achieved within 3–5 min after withdrawal of ventilatory support; at this point the patient should be reconnected to the ventilator (or earlier, should hemodynamic instability, desaturation, or spontaneous breathing movements occur).
   f. Arterial blood gas sampling immediately before reinstitution of mechanical ventilation to confirm the $paCO_2$ rise to >60 mm Hg.
   g. Criteria for positive apnea test: No evidence of spontaneous respirations before reinstitution of mechanical ventilation in the presence of $paCO_2$ >60 mm Hg or $paCO_2$ increase of >20 mm Hg from the normal baseline value.

(continue)

TABLE 132-1 Brain Death Criteria and Clinical Diagnosis of Brain Death *(continued)*

5. Confirmatory tests should be used when the observation period needs to be shortened (e.g., unstable donors); in equivocal situations (including age younger than 1 year); or if one of the potential pitfalls (Table 132-2) cannot be ruled out. Tests must demonstrate absence of intracranial circulation by angiographic contrast or radioisotopic flow studies, transcranial Doppler ultrasonography, or electrocerebral silence documented by an electroencephalogram. Pursue DCD if the patient is unconscious, has suffered significant irreversible brain injury, but does not fulfill all formal criteria for brain death, and if patient's family wishes to withdraw technology.

TABLE 132-2 Pitfalls in Clinical Brain Death Testing and Potential Remedial Measures

Pitfalls	Remedial measure(s)
Hypotension, shock	Institute fluid resuscitation, use pressor agents
Hypothermia	Use warming blanket, warmed fluids, heated ventilator gases
Intoxication or drug overdose	If measurable, check drug levels and toxicology screens or increase waiting time between brain death examinations, administer specific antidotes (e.g., naloxone, flumazenil)
Neuromuscular and sedative drugs, which can interfere with elicitation of motor responses	Discontinue muscle relaxants and mood- or consciousness-altering medications, increase waiting time between brain death examinations
Pupillary fixation, which may be caused by anticholinergic drugs (e.g., atropine given during a cardiac arrest), neuromuscular blocking agents, or preexisting disease	Discontinue anticholinergic medications and muscle relaxants, increase waiting time between brain death examinations, obtain careful patient history
Corneal reflexes absent due to overlooked contact lenses	Remove contact lenses before brain death examination
Oculovestibular reflexes diminished or abolished after prior use of ototoxic drugs (e.g., aminoglycosides, loop diuretics, vancomycin) or agents with suppressive side effects on the vestibular system (e.g., tricyclic antidepressants, anticonvulsants, and barbiturates) or due to preexisting disease	Obtain careful medication history and patient history

B. Consent rates are highest when an OPO representative or an OPO-designated requestor broaches the possibility of organ donation with the family.

C. Other important factors affecting the decision to donate include level of education, understanding and awareness of the irreversibility of severe brain injury (DCD donors) and of brain death, amount of time spent by the OPO representative with the family, and covering discussion topics of importance to donor families (e.g., costs, funeral, choices regarding amount of tissue/organs donated).

VI. PERIOPERATIVE CARE OF THE BRAIN-DEAD ORGAN DONOR

A. General considerations.

1. Once consent for organ donation is obtained, the focus switches from cerebral protection to preservation of organ function and optimization of peripheral oxygen delivery.

2. Inadequate brain-dead donor management may result in loss of transplantable organs or even (in up to 15%) loss of the organ donor altogether.

3. Pathophysiology of brain death maintenance phase.

a. Loss of central temperature control mechanisms leading to hypothermia.

b. Hypotension due to complete arterial and venous vasomotor collapse.

c. Abolition of resting vagal tone secondary to destruction of the nucleus ambiguus, eliminating all chronotropic effects of atropine.

d. Absence of pituitary hormones (including vasopressin).

e. Upregulation of proinflammatory and immunoregulatory pathways.

B. Management principles.

1. Monitoring.

a. Core temperature, central venous pressure (CVP), systemic arterial blood pressure (arterial line), pulmonary artery (PA) catheter in selected donors, and pulse oximetry.

b. Foley catheter to monitor urine output.

c. Frequent determination of electrolytes and arterial blood gases.

d. Regular monitoring (every 12 hours) of blood urea nitrogen (BUN) and creatinine level, liver enzymes, amylase, lipase, and coagulation tests to help assess organ status and function.

2. Maintenance therapy end points in brain-dead organ donors.

a. Systolic blood pressure 100 to 120 mm Hg, mean arterial pressure (MAP) > 60 mm Hg.

b. CVP 8 to 10 mm Hg.

c. Systemic vascular resistance (SVR) 800 to 1,200 dyne/s/cm^5.

d. Dopamine <10 μg/kg/min.

e. Urine output 100 to 300 mL/h.

f. Core temperature >35°C.

g. paO_2 80 to 100 mm Hg, Sao_2 >95%, pH 7.37 to 7.45.

h. Hemoglobin 10 to 12 g/dL, hematocrit 30% to 35%.

TABLE 132-3 Differential Diagnosis of Hypotension in the Brain-Dead Organ Donor

Hypovolemia
Hypothermia
Cardiac dysfunction
Arrhythmia (ischemia, catecholamines, hypokalemia, hypomagnesemia)
Acidosis
Hypo-oxygenation
Excessive positive end-expiratory ventilatory pressure
Congestive heart failure due to excessive fluid administration
Hypophosphatemia
Hypocalcemia
Causes related to the injury that caused brain death (cardiac tamponade, myocardial contusion)
Myocardial sequelae of autonomic storm during brain herniation
Preexisting cardiac disease
Pneumothorax (traumatic or iatrogenic)
Drug side effects or overdose (e.g., long-acting β-blocker, calcium channel antagonist, antihypertensive agent)

3. Cardiovascular support.
   a. Hypotension: most common, usually due to hypovolemia, but there are many other potential diagnoses (Table 132-3). If hypotension persists despite euvolemia, administer dopamine or α-adrenergic agents (e.g., phenylephrine), and consider use of arginine vasopressin and T3 (see dosages below under "Hormonal/endocrine support") to reduce catecholamine requirements.
   b. Hypertension: treat with short-acting vasodilatory agents (e.g., sodium nitroprusside) or short-acting β-blockers.
4. Respiratory support.
   a. Vigorous tracheobronchial toilet with frequent suctioning; aspiration precautions.
   b. Positive end-expiratory pressure (PEEP) at 5 cm H_2O, tidal volumes 8 to 10 mL/kg, peak airway pressures <30 cm H_2O. For potential lung donors, CVP should be kept at 6 to 8 mm Hg, PA balloon occlusion pressure at 8 to 12 mm Hg.
   c. Steroid bolus treatments during the maintenance phase may exert potential beneficial effects (improved oxygenation and increased donor lung recovery rates; see dosage below under "Hormonal/endocrine support").
5. Renal function and electrolyte management.
   a. Goals (for potential kidney donors).
      i. Maintain adequate systemic arterial perfusion pressure.
      ii. Maintain brisk urine output (>1 to 2 mL/kg/h).
      iii. Insufficient urine production (<1 mL/kg/h) after adequate resuscitation: administer loop or osmotic diuretics (furosemide, mannitol).
      iv. Avoid nephrotoxic drugs.

b. Polyuria.
  i. Frequently observed in brain-dead donors.
  ii. Etiologies.
    (a) Osmotic diuresis (induced by mannitol administered to decrease intracranial pressure (ICP) during prebrain death phase or hyperglycemia).
    (b) Hypothermia.
    (c) Diabetes insipidus.
      (1) Diagnosis.
        - Urine volumes >200 mL/h (or >5 mL/kg/h) for two consecutive hours with hypernatremia (serum sodium >147 mEq/L), elevated serum osmolality (>310 mOsm/kg), and a low urinary sodium concentration.
        - Not infrequently associated with other electrolyte abnormalities: hypokalemia, hypocalcemia, or hypomagnesemia.

      (2) Treatment.
        - Vasopressin or vasopressin analogues (indicated once urine output exceeds 300 mL/h). Desmopressin (desamino-8-D-arginine vasopressin [DDAVP]) has a long duration of action and high antidiuretic-to-pressor ratio, reducing undesirable splanchnic vasoconstrictor effects of arginine vasopressin. Dosage: 1 to 2 μg desmopressin are administered IV every 8 to 12 hours to titrate urine output to values of 100 to 300 mL/h.
        - Correct hypernatremia: Use infusion solutions with low or no sodium content (e.g., D5W solution [free water]). Take into consideration sodium content of other IV fluids (e.g., of 5% albumin solutions).
        - Adjunct measures: correct coexisting hypovolemia/water deficit and hyperglycemia, discontinue mannitol.

6. Hypothermia.
  a. After brain death, when the body becomes poikilothermic because of the loss of central temperature control mechanisms, hypothermia is further aggravated by peripheral vasodilatation. Hypothermia is observed in up to 80% of brain-dead bodies.
  b. Adverse effects: Decreased myocardial contractility, hypotension, cardiac arrhythmias, cardiac arrest, hepatic and renal dysfunction, acidosis, or coagulopathy.
  c. Therapy: Maintain donor core temperature at >35°C using warmed IV fluids and blood products, warming blankets, or heated ventilator gases.

7. Coagulation system.
  a. Coagulopathy and disseminated intravascular coagulation are common findings in brain-dead donors, particularly after head injury.
  b. Clinical findings: pathologic bleeding, abnormal prothrombin time (PT)/international normalized ratio (INR), thrombocytopenia, hypofibrinogenemia, increased fibrin/fibrinogen degradation products.
  c. Treat coagulopathy using blood products as indicated by specific findings. Correct underlying pathophysiology (e.g., hypothermia, acidosis).

8. Hormonal/endocrine support.
   a. Hyperglycemia.
      i. Frequent in brain-dead donors.
      ii. Etiologies.
         (a) Increased catecholamine release.
         (b) Altered carbohydrate metabolism.
         (c) Steroid administration for treatment of cerebral edema.
         (d) Infusion of dextrose-containing IV fluids.
         (e) Peripheral insulin resistance.
      iii. Treatment: insulin (subcutaneously or continuous IV infusion) to maintain glucose levels at 100 to 180 mg/dL.
      iv. Good glycemic control also prevents ketoacidosis and osmotic diuresis and may be beneficial for quality of early posttransplant pancreas graft function.
   b. Routine hormonal support may stabilize and improve cardiac function in hemodynamically unstable or otherwise marginal brain-dead donors and may result in increased probability of kidney, heart, liver, lung, and pancreas recovery and transplantation (available data are not conclusive and await confirmation in prospective controlled trials). Nonetheless, the American Society of Transplant Surgeons and American Society of Transplantation 2002 Consensus Conference Recommendations on donor hormonal support are widely used.
      i. Triiodothyronine (T3: 4 μg bolus, 3 μg/h continuous IV infusion) (effects: reversal of myocardial dysfunction, improved arterial pressure, decreased CVP, significant reduction of inotropic requirements).
      ii. Methylprednisolone: 15 mg/kg/bolus IV (repeat every 24 hours) (effects: improved oxygenation and increased donor lung recovery; putative beneficial effects in the donor and the organ recipient from attenuation of the effects of proinflammatory cytokines released as a consequence of brain death).
      iii. Arginine vasopressin: one unit IV bolus, followed by 0.5 to 4.0 units/h IV continuous infusion (titrate SVR to 800 to 1,200 dyne·sec·cm^{-5} if PA catheter in place) (effects: treatment of diabetes insipidus, reduces inotropic requirements; better kidney, liver, and heart graft function; beneficial hemodynamic effects are present even in unstable patients who do not have diabetes insipidus).

C. Intraoperative care.

1. In brain-dead donors, full cardiovascular and ventilatory support is maintained throughout the donor operation until aortic cross-clamp and onset of the organ flush phase.
2. Maintain hemodynamic stability and ensure adequate fluid resuscitation, particularly in thoracic and abdominal organ donors when both body cavities are open and significant evaporative and massive third space fluid losses can occur.
3. Maintain normothermia.

VII. PERIOPERATIVE CARE OF THE DONATION AFTER CARDIAC DEATH DONOR

A. Preoperative care of potential DCD donors (prior to obtaining consent for organ donation).

1. Focus treatment on the underlying pathology (e.g., head trauma, CVA).

B. Preoperative care of actual DCD donors (after having obtained consent for organ donation).

1. The focus switches from cerebral protection to preservation of organ function and optimization of peripheral oxygen delivery.
2. Maintenance therapy end points are identical to those described above for brain-dead organ donors.

C. Intraoperative care of DCD donors.

1. Maintenance therapy is continued until support is withdrawn and the patient is extubated.
2. Additional premortem interventions (e.g., surgical: insertion of femoral cannulas in preparation of organ recovery; pharmacologic: administration of intravenous heparin, opioids, and phentolamine) must occur in strict accordance with local OPO/hospital DCD protocols and policies.
3. Death is pronounced by a physician not belonging to the organ recovery and transplant team (usually the patient's intensive care physician).
4. After an additional postmortem waiting time (minutes) specified by the local OPO/hospital DCD protocol, surgical organ recovery begins.
5. Disposition of the patient, if death does not occur within a specified waiting time after withdrawal of support, is determined by the local protocol (e.g., return patient to a non–intensive care hospital floor for comfort focused care [see also Chapter 23]).

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133 Rejection, Infection, and Malignancy in Solid Organ Transplant Recipients

Brian J. Gallay

REJECTION

I. GENERAL PRINCIPLES

Solid organ donor antigens are recognized by the recipient immune system, resulting in acute and chronic rejection. Immunosuppression minimizes the effects of rejection in order to prolong graft function.

II. PATHOGENESIS

A. Highly polymorphic human leukocyte antigens (HLAs) and peptide antigens derived from other cellular proteins are presented by antigen-presenting cells to the immune effector cells of the recipient.

B. Acute rejection: unrestricted activation and proliferation of recipient immune cells. If not treated immediately, permanent graft dysfunction or loss occurs.

C. Chronic rejection: longer term irreversible graft fibrosis.

III. DIAGNOSIS

Rule out other causes of allograft dysfunction. Confirm with biopsy before specific therapy or as soon as possible after empiric therapy is begun.

A. Kidney: decreased urine output, elevated serum creatinine, proteinuria >200 mg/day.

Rule out:

1. Intravascular volume depletion (response to IV saline bolus).
2. Ureteral obstruction or urine leak (ultrasound).
3. Arterial or venous obstruction or thrombosis (Doppler ultrasound).
4. Drug nephrotoxicity.
5. Infection, including adenovirus, cytomegalovirus (CMV), polyomavirus nephropathy.

B. Liver: elevated serum transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), gamma glutamyltransferase (GGT), alkaline phosphatase, bilirubin.

Rule out:

1. Hepatic artery thrombosis (particularly early postoperatively; Doppler ultrasound).

2. Biliary obstruction (ultrasound).
3. Drug hepatotoxicity.
4. Liver graft infection, most commonly viral, that is, CMV; hepatitis C virus (HCV) or hepatitis B virus (HBV) (primary infection or disease recurrence in the liver graft).
5. Functional cholestasis (e.g., due to sepsis, cholangitis).
6. Intravascular volume depletion.

C. Heart: decreased left ventricular ejection fraction (symptoms of congestive heart failure, echocardiogram), acute myocardial infarction (associated with chronic rejection).

Rule out:

1. Infection (CMV, toxoplasmosis).
2. Posttransplant lymphoproliferative disease (PTLD) (serum Epstein-Barr virus [EBV] PCR and biopsy).

D. Lung: cough, shortness of breath, decreased forced expiratory volume in 1 second (FEV_1) on pulmonary function testing.

Rule out:

1. Infection (pleural fluid analysis and culture, bronchoalveolar lavage, transbronchial biopsy).
2. Airway stenosis at bronchial anastomosis, airway granulation tissue (bronchoscopy).
3. Thromboembolism (ultrasound to rule out deep venous thrombosis, CT angiogram, D-dimer).
4. Recurrence of original disease.

E. Pancreas: elevated serum amylase; decreased urinary amylase excretion (with bladder-drained pancreas grafts). Hyperglycemia is a late manifestation.

Rule out:

1. Vascular thrombosis (Doppler ultrasound).
2. Leak from enteric anastomosis (duodenojejunostomy, enteric-drained grafts) or bladder anastomosis (duodenocystostomy, bladder-drained grafts); diagnosis by ultrasound, CT, or cystography (bladder-drained grafts).
3. Pancreatic duct obstruction magnetic resonance cholangiopancreatography (MRCP).
4. Recurrence of type 1 diabetes mellitus.

F. Intestine: increased stoma output, ileus, fever, abdominal distension and pain, decreased oral intake.

Rule out:

1. Bacterial or fungal sepsis (can also be precipitated by acute rejection).

IV. THERAPY

A. Maintenance of immunosuppression.

1. Corticosteroids decrease antigen presentation and lymphocyte activation.
2. Calcineurin inhibitors (cyclosporine, tacrolimus) block cytokine interleukin (IL)-2 production to inhibit T-cell activation.
3. Antimetabolites (mycophenolate mofetil, azathioprine) inhibit T- and B-lymphocyte proliferation.

4. mTOR inhibitors (sirolimus, everolimus) inhibit initiation of T-cell proliferation.
5. Belatacept inhibits T-cell activation by blocking costimulatory molecule interactions.
6. Antilymphocyte serum and alemtuzumab deplete lymphocytes from the circulation.
7. Basiliximab binds to the IL-2 receptor to inhibit T-cell activation.
8. Rituximab depletes B-cells.

B. Acute rejection.

1. Corticosteroid pulse: up to 8 mg/kg methylprednisolone daily for 3 days.
2. Lymphocyte depletion: for example, Thymoglobulin 1.5 mg/kg daily for at least five doses.
3. Rituximab, intravenous immunoglobulin (IVIG), and plasmapheresis to treat acute antibody-mediated rejection.

C. Chronic rejection: Increase maintenance immunosuppression if possible.

V. COMPLICATIONS

A. Infection and malignancy (see sections on Infection and Malignancy below).

B. Drug toxicities and side effects.

1. Corticosteroids: hypertension, edema, hyperglycemia, obesity, osteoporosis, dyslipidemia.
2. Cyclosporine and tacrolimus: acute kidney injury, hypertension, neurotoxicity, diabetes, dyslipidemia, hemolytic uremic syndrome.
3. Antimetabolites: leukopenia, anemia, thrombocytopenia, liver failure, diarrhea.
4. Sirolimus and everolimus: anemia, thrombocytopenia, leukopenia, proteinuria, diabetes, oral ulcers, edema, synovitis.
5. Belatacept: central nervous system (CNS) lymphoma.
6. Antilymphocyte globulin and alemtuzumab: leukopenia, thrombocytopenia, fever, hypotension, pulmonary edema.

INFECTION

I. GENERAL PRINCIPLES

A. Immunosuppression impairs recognition and clearance of infection, particularly by T-lymphocytes. Time elapsed since transplant, intensity of immunosuppression, and the epidemiologic exposures of the individual patient all influence the types of infection that can develop.

B. Different allografts have unique risks for infection.

1. Lung transplant recipients may be colonized with multiply-resistant gram-negative pathogens, *Aspergillus* spp., or mycobacteria, due to impaired mucociliary clearance and chronic lung disease.
2. Surgical technique (e.g., enteric vs. bladder drainage for pancreas grafts, and Roux-en-Y hepaticojejunostomy vs. choledochocholedochostomy for liver grafts) may predispose to different bacterial or fungal infections.

3. Prior management with left ventricular assist devices may predispose heart transplant recipients to infections with nosocomial, resistant organisms.

II. PATHOGENESIS

A. Nosocomial infection (<1 month posttransplant).

1. Aspiration pneumonia.
2. Wound infection.
3. Vascular or urethral catheter infection.
4. Anastomotic leak (urinary, biliary, intestinal).
5. Recipient-derived, prior colonization: *Aspergillus*, *Pseudomonas.*
6. Consider antibiotic-resistant organisms: MRSA, VRE, non-albicans *Candida.*

B. Donor-derived (often within 1 month posttransplant but can occur later): herpes simplex virus (HSV), HIV, West Nile virus, rabies, *Trypanosoma cruzi.*

C. Reactivation of latent opportunistic infections (1 to 6 months posttransplant).

1. *Pneumocystis jirovecii* pneumonia (especially if no trimethoprim-sulfamethoxazole prophylaxis).
2. Herpesviruses: HSV, EBV, CMV, varicella zoster virus (VZV) (especially if no antiviral prophylaxis).
3. *Nocardia* spp., *Listeria monocytogenes*, *Toxoplasma gondii*, *Strongyloides stercoralis*, *Leishmania*, *T. cruzi*, *Cryptococcus neoformans.*
4. Mycobacterium (*Mycobacterium tuberculosis*, atypical mycobacteria).

D. Community-acquired infection (>6 months posttransplant).

1. Community-acquired respiratory infections: typical bacterial pathogens, viruses (influenza, respiratory syncytial virus [RSV], parainfluenza, adenovirus).
2. Community-acquired urinary tract infection (UTI).
3. Opportunistic infections: *Aspergillus* spp., *Mucor* spp., *Nocardia.*
4. Herpesviruses: late-onset CMV disease (viremia, gastritis, enterocolitis, hepatitis), HSV (encephalitis and esophagitis), VZV reactivation (shingles).
5. Endemic mycoses: Coccidioidomycosis, histoplasmosis, blastomycosis.
6. Exposures related to recent and distant travel. Obtain detailed history.

E. *Clostridium difficile* colitis: can present at any time posttransplant, can be refractory to standard treatment courses, and can be relapsing, requiring prolonged or tapering courses of treatment.

III. DIAGNOSIS

A. See Chapter 67 for details on the evaluation of infection in the Immunocompromised Host.

B. Consider time elapsed since transplant to suggest most likely infections and to target evaluation.

C. Physical examination may be affected by immunosuppression effect on inflammatory symptoms. Consider atypical and more severe presentations.

D. Viral PCR assays that should always be considered to include CMV and EBV PCR.
E. Early tissue diagnosis is crucial.

IV. THERAPY

A. Begin broad-spectrum therapy immediately after cultures are obtained.
B. Narrow coverage to usual standards, when definitive diagnosis is made.
C. Duration of therapy is often longer than for immunocompetent hosts and is guided by surveillance culture, antigen assay, or PCR.
D. Reduce or discontinue immunosuppression based on the severity of infection. Resume after definitive anti-infectious therapy is begun and titrate up carefully.

MALIGNANCY

I. GENERAL PRINCIPLES. Malignancy is a common cause of death in transplant recipients. Acute manifestations can be immediately life-threatening.

II. PATHOGENESIS

A. Recurrence of a previously treated malignancy: melanoma, breast, colon.
B. Decreased immune surveillance.
   1. Decreased numbers and activation of T-lymphocytes; persistence of transformed cells.
   2. Skin cancer is the most common form of posttransplant malignancy due to combination of UV radiation and increased persistence of premalignant cells.
      a. Decreased ability to control growth and metastasis of tumors can lead to widespread metastasis at the time of first presentation, as for example, with melanoma.
   3. Viral infection.
      a. PTLD: EBV infection of B-lymphocytes, presenting as lymphadenopathy, mass in CNS, intestine, or allograft.
      b. Kaposi sarcoma: human herpes virus (HHV)-8 infection of lymphatic and blood vascular endothelial cells.

III. DIAGNOSIS

A. Frequent dermatologic evaluation for skin cancer and removal of suspicious lesions.
B. Physical examination for lymphadenopathy, mass lesions in oropharyngeal mucosa, hepatosplenomegaly, abdominal masses.
C. Imaging for mediastinal lymphadenopathy, CNS mass lesions, abdominopelvic masses.
D. Serum PCR for viral infection (EBV, HHV-8).
E. Biopsy of mass lesion, bronchoalveolar lavage/transbronchial biopsy, colonoscopy, cytology of pleural fluid or ascites, bone marrow biopsy (PTLD).

IV. THERAPY

A. Usual therapy with surgery, radiation, and/or chemotherapy as indicated. Metastatic disease at presentation confers a worse prognosis.

B. Decrease or discontinue immunosuppressive therapy, depending on the type of allograft and severity of disease.

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134 Critical Care of Kidney Transplant Recipients

Brian J. Gallay

I. GENERAL PRINCIPLES

Patients with chronic kidney disease have multiple comorbidities that affect transplant outcomes. Consider underlying disease to guide pretransplant evaluation and postoperative management.

II. IMMEDIATE PRETRANSPLANT EVALUATION

A. Cardiovascular assessment.

1. Assess history of coronary artery disease, symptoms of angina or congestive heart failure, recent change in exercise tolerance, new ischemic changes on ECG, decreased pulse or bruit, or pathologic heart murmur on physical examination.
2. Prevention.
   a. Continue perioperative β-blocker therapy for patients already on β-blockers. Monitor for hyperkalemia, bradycardia, and hypotension.
   b. Continue or start aspirin if bleeding risk is acceptable.
   c. Continue clopidogrel to minimize risk of drug-eluting stent thrombosis.

B. Infectious disease assessment.

1. Assessment: Obtain history of recent febrile illness or recurrent infection. Examine for signs or symptoms of active infection, including lymph nodes, oral mucosa, skin (especially intertrigal areas and feet), hemodialysis or peritoneal dialysis catheters, and hemodialysis access grafts. Obtain peritoneal fluid sample from peritoneal dialysis catheter for cell count and culture. Peripheral blood neutrophil count and urinalysis for evidence of active infection. Check chest radiograph for mass, nodules, or cavitary lesions.
2. Prevention: Postpone transplant if active infection is identified. Use routine preoperative antibacterial prophylaxis.

C. Malignancy assessment.

1. Careful skin examination for melanoma.
2. Oral examination for squamous cell epithelial cancer.
3. Complete lymph node examination.

D. Preoperative dialysis assessment.
1. Assess volume status, looking for jugular venous distension, pulmonary and peripheral edema.
2. Dialyze for (i) hypervolemia to minimize risk of postoperative pulmonary edema and hypertension, and (ii) hyperkalemia (K^+ >5 mEq/L) to minimize risk of cardiac arrhythmia.

E. Other issues.
Determine and document pretransplant urine output to facilitate interpretation of postoperative kidney graft function.

III. INTRAOPERATIVE CARE

A. Avoid hypotension that impairs perfusion and increases risk of delayed graft function (i.e., need for dialysis therapy during the first week after transplant).
B. Maintain euvolemia. Use central venous pressure (CVP) monitoring to maintain CVP at 5 to 10 cm H_2O.
C. Consider pulmonary artery catheterization to assess hemodynamics in patients with decreased left ventricular function or pulmonary hypertension.

IV. PERIOPERATIVE CARE

A. Obtain postoperative chest radiograph to evaluate pulmonary status.
B. Doppler ultrasound to assess kidney graft perfusion.
C. Monitor electrolytes every 6 to12 hours in the first 24 hours.
1. Urine output can reach 1 L/hour, requiring frequent fluid and electrolyte replacement.

D. Carefully monitor fluid balance in oliguria (urine output ≤20 mL/hour). Minimize IV fluids if hypervolemic, and rule out urinary obstruction, vascular thrombosis, or acute rejection. Give a short diuretic trial if hypervolemic or IV saline bolus if hypovolemic.

V. POSTOPERATIVE CONSIDERATIONS

A. Surgical complications.
1. Hemorrhage.
   a. Has been reported to occur in as many as 12% of recipients.
   b. Increased risk if transplant must be done on aspirin and/or clopidogrel, and if preoperative reversal of warfarin anticoagulation is required.
   c. Consider vascular anastomotic bleeding and early surgical reexploration. But in >50% of cases no obvious source of bleeding is identified.
2. Kidney graft thrombosis.
   a. Risk factors.
      i. Hypotension and hypovolemia.
      ii. Hypercoagulable state (antiphospholipid antibody; protein C, S, or antithrombin III deficiency; factor V Leiden mutation).

iii. Peripheral vascular disease (occlusion by intimal flap or thrombosis).
iv. Multiple small renal arteries, or pediatric donor.

b. Diagnosis and treatment.
i. Sudden oliguria (arterial thrombosis), gross hematuria, kidney graft pain, and swelling (venous thrombosis).
ii. Doppler ultrasound demonstrates absence of flow in the renal artery or vein.
iii. Almost always requires graft nephrectomy.

c. Prevention.
i. Maintain adequate blood pressure and intravascular volume.
ii. Aspirin for severe peripheral vascular disease.
iii. IV heparin for hypercoagulable state. Therapeutic target partial thromboplastin time (PTT) 1.5 to 1.9 times the upper limit of normal range is suggested. Warfarin therapy should be initiated for at least 3 months.

3. Urologic.
a. Persistent gross hematuria, usually from the ureteroneocystostomy. Use continuous bladder irrigation; avoid high-pressure catheter flushes.
b. Urinary leak due to anastomotic complication or distal ureteral necrosis can present with oligoanuria or significant increase in wound drainage.
i. Diagnosis: high creatinine level in wound drainage fluid suggests urine leak; ultrasound may identify perigraft fluid collection (urinoma); nuclear scan may identify extravasation of tracer from ureter; percutaneous nephrostogram can provide definitive diagnosis.
ii. Treatment: decompression and external drainage by placement of Foley catheter and percutaneous nephrostomy with or without nephroureteral stent. Leaks not amenable to nonoperative treatment require surgical revision and ureteral reimplantation.

4. Wound.
a. Infection and wound dehiscence are infrequent (<5%). Obesity (body mass index >30 kg/m^2) and sirolimus, which impairs wound healing, increase risk.
b. Symptomatic lymphocele occurs in up to 5%, presenting with ureteral or venous obstruction, often with ipsilateral lower extremity edema. Definitive treatment is laparoscopic internal drainage through a peritoneal window.

B. Medical complications.

1. Cardiovascular.
a. Maintain a high index of suspicion for acute coronary syndrome, especially with postoperative hypotension, pulmonary edema, or arrhythmia.
b. Consider pulmonary embolism in the presence of acute respiratory decompensation.
c. Consider atheroembolism in patients with sudden kidney graft dysfunction.

2. Metabolic.
   a. Treat hyperkalemia with calcium chloride, insulin, and dextrose, inhaled beta-agonists, and sodium bicarbonate, followed by forced diuresis or dialysis.
   b. Hypocalcemia, hypophosphatemia, and hypomagnesemia can occur with polyuria. Frequent monitoring (every 6 to 12 hours) and repletion are required.
3. Infection: Bacterial or fungal early postoperative infection is most common.
4. Neurologic.
   a. Consider stroke in the setting of unexplained altered level of consciousness or focal neurologic changes. Evaluate with head CT without contrast.
   b. New-onset seizure is uncommon. Rule out uremia, stroke, or drug toxicity.
   c. Encephalopathy may be due to uremia or drugs, especially tacrolimus.

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135 Critical Care of Pancreas Transplant Recipients

Christoph Troppmann

I. GENERAL PRINCIPLES

A. Currently, pancreas transplantation is the only diabetes treatment that consistently normalizes glycosylated hemoglobin (HbA1c) levels, positively influences the progression of secondary diabetic complications, significantly ameliorates quality of life, and may prolong life. Most pancreas transplants are performed for selected, medically suitable patients with type I diabetes. Type II diabetes remains a relatively infrequent indication (<10% of all pancreas transplants).

B. Depending on the recipient's native kidneys' functional status, pancreas transplants are performed in three recipient categories.

1. Simultaneous pancreas–kidney transplants (SPKs) in preuremic and uremic patients.
2. Pancreas after kidney transplants (PAKs) in posturemic recipients of a previous kidney transplant (from a deceased or a live donor).
3. Pancreas transplants alone (PTA) in nonuremic recipients with extremely labile diabetes but adequate native renal function.

C. Pancreas graft survival rates have significantly improved and now exceed 90% at 1 year and 80% at 5 years (SPK).

II. IMMEDIATE PRETRANSPLANT EVALUATION

Patients admitted to the hospital for pancreas transplantation must be evaluated for the following risk factors for adverse perioperative outcomes.

A. Coronary artery disease. Diabetics (those with and without end-stage renal disease [ESRD]) have a high incidence of coronary artery disease. In the course of their transplant workup, prospective pancreas transplant recipients will have been screened for coronary artery disease by noninvasive tests or coronary angiography. Immediately preoperatively, particular attention must be paid to new symptoms of angina, congestive heart failure, recent changes in exercise tolerance, and new, possibly ischemic, changes on the ECG.

B. Peripheral vascular disease. Assess for decreased peripheral pulses or new bruits on peripheral vascular examination, when compared to baseline. Infected diabetic foot ulcers are generally a contraindication to transplantation. Check also for new signs and symptoms of stroke and ischemic cerebrovascular disease.

C. Infectious disease. Diabetes in combination with uremia is a significant risk factor for infection. Preoperative evaluation must include chest radiograph, urinalysis, and careful assessment of indwelling catheters and catheter exit sites (hemodialysis catheters, peritoneal dialysis catheters [including a peritoneal fluid cell count and culture]) and of vascular access grafts. Active infection is a contraindication to transplantation.

D. Metabolic and fluid status. Hyperkalemic uremic patients admitted for transplant may need therapy before the transplant operation (e.g., oral sodium polystyrene sulfonate, intravenous [IV] insulin and glucose, dialysis). Hypervolemic recipients may also need preoperative dialysis. Hyperglycemia with metabolic acidosis requires preoperative correction.

E. Absolute contraindications to transplantation.

1. Active sepsis.
2. Active viral infection.
3. Malignancy (except if treated, nonmetastatic, without recurrence, and with sufficient posttreatment follow-up).

III. INTRAOPERATIVE CONSIDERATIONS

A. Operative technique.

1. All pancreas transplants currently performed are from deceased donors and entail transplantation of the entire organ with an attached segment of duodenum that serves as the conduit for the exocrine secretions.
2. Management of pancreatic exocrine secretions. Usually, the exocrine secretions are drained enterically via an anastomosis of the graft's duodenal segment to the recipient's small intestine (duodenoenterostomy, performed in >90% of all pancreas transplants). For PAK and PTA recipients, bladder drainage (creation of a duodenocystostomy) can provide a useful additional means to monitor for rejection (by measuring urinary amylase).
3. Venous pancreas graft drainage. The venous effluent of the pancreas graft can be drained systemically, into an iliac vein or the inferior vena cava (performed in >80% of all pancreas transplants), or portally, into the superior mesenteric vein. Portal drainage has theoretical, but clinically to date unproved advantages (host tolerance facilitation by portally delivered graft antigen; avoidance of potential sequelae of systemic hyperinsulinemia).

B. Cardiovascular care and monitoring.

1. Recipients may benefit from perioperative cardioprotection with β-blockers.
2. Hemodynamic monitoring: central venous pressure (CVP) catheter; arterial line and pulmonary artery catheter only if indicated (e.g., presence of moderate left ventricular dysfunction).
3. Maintain adequate intravascular volume status, avoiding high CVPs that can predispose pancreas grafts with systemic venous drainage to edema while providing adequate preload for optimal perfusion of the kidney graft (SPK recipients). Judicious fluid management to avoid fluid overload and acute myocardial strain is paramount.

C. Foley catheter, nasogastric tube.

D. Metabolic care. Frequent (at least hourly) intraoperative monitoring of blood glucose levels is important, because the pancreas graft often begins to function immediately postreperfusion, resulting in decreasing blood glucose levels and no further need for exogenous insulin.

IV. POSTOPERATIVE CARE

A. General: Immediate postoperative chest radiograph and frequent monitoring of blood glucose and electrolyte levels; daily serum amylase and lipase levels.

B. Metabolic.

1. In the few grafts that have delayed function, temporary administration of exogenous insulin may be necessary (initially, most easily by IV insulin infusion with hourly blood glucose monitoring; adjust infusion rate to maintain blood glucose levels 80 to 120 mg/dL).
2. Bladder-drained recipients must be monitored closely for fluid and electrolyte losses from the exocrine pancreas, which can result in dehydration and metabolic acidosis. Urine is collected over an 8-hour period on each postoperative day, and hourly urinary amylase production (expressed as amylase units/hour) is determined. With normal pancreas graft recovery from preservation and reperfusion injury, urinary amylase excretion should increase daily before reaching its baseline, usually after discharge of the recipient from the hospital.

C. Kidney graft monitoring and management (see Chapter 134).

D. Provision of adequate immunosuppression.

1. Immunosuppression may include a combination of any of the following: polyclonal or monoclonal anti–T-cell agents for induction therapy during the first week (e.g., antithymocyte globulin, alemtuzumab [T-cell–depleting induction] or basiliximab [nondepleting induction]), steroids, calcineurin inhibitors (tacrolimus, cyclosporine), mycophenolate mofetil, mTOR inhibitors (sirolimus, everolimus).
2. Solitary pancreas transplants (PAK and PTA) are more immunogenic and do not have a kidney from the same donor (as SPK recipients do) that would more easily allow for rejection monitoring (i.e., by checking serum creatinine levels). They require, therefore, closer surveillance for rejection and often more induction and maintenance immunosuppression.

E. Antimicrobial prophylaxis.

1. IV broad-spectrum antibiotics for 3 to 5 days (e.g., cephalosporins).
2. Antifungal prophylaxis with fluconazole for 1 to 6 weeks, depending upon programmatic protocols.
3. *Pneumocystis jirovecii* prophylaxis with trimethoprim–sulfamethoxazole for up to 1 year.
4. Cytomegalovirus (CMV) prophylaxis for 1 to 6 months (depending on donor–recipient CMV serostatus); duration of prophylaxis depending upon programmatic protocols.

F. Graft thrombosis prophylaxis.

1. No prospective data are available to support current empiric practices.
2. Some transplant programs perioperatively anticoagulate recipients subtherapeutically for the first 3 to 7 days (e.g., heparin infusion at 300 to 700 units/hour IV). Some of these recipients are then orally anticoagulated with warfarin for the first 6 months.
3. Many transplant programs start recipients perioperatively on oral aspirin, which is continued indefinitely.

V. POSTOPERATIVE CONSIDERATIONS

A. Surgical complications.

1. Postoperative bleeding.
   a. Diagnosis: by serial hemoglobin/hematocrit levels; hemodynamic changes (hypotension, tachycardia, decreased CVP, decreased left ventricular filling pressures).
   b. Most common bleeding sources: free intra-abdominal bleeding from the graft itself or the vascular anastomoses; gastrointestinal bleeding manifesting as lower GI bleeding (from the duodenoenteric anastomosis in enteric-drained grafts); intravesical bleeding with massive hematuria (from the duodenovesical anastomosis in bladder-drained grafts).
   c. Check platelets, prothrombin time (PT)/INR, and partial thromboplastin time (PTT). Replace coagulation factors and platelets as indicated.
   d. For ongoing intra-abdominal bleeding, relaparotomy for hemostasis and evacuation of hematoma may be necessary.
2. Pancreas graft thrombosis.
   a. Most frequent serious surgical complication (incidence: 5% to 10%); nearly always results in graft loss.
   b. Symptoms. Sudden onset of otherwise unexplained hyperglycemia (arterial and/or venous thrombosis); graft tenderness and enlargement (venous thrombosis); dark, massive hematuria (venous thrombosis of bladder-drained pancreas grafts); markedly decreased or absent urinary amylase on spot urinary amylase check (bladder-drained grafts).
   c. Diagnosis.
      i. Imaging studies: Doppler duplex ultrasonography, computed tomographic angiography, magnetic resonance angiography, graft scintigraphy, conventional angiography.
      ii. Diagnosis made during exploratory relaparotomy.
   d. Treatment: Transplant pancreatectomy required for nearly all cases of complete graft thrombosis.
3. Surgical wound infection.
   a. Superficial wound infection.
      i. Symptoms: fever, wound drainage, cellulitis, leukocytosis.
      ii. Treatment: IV antibiotics and local incision and drainage; open wound care with daily dressing changes.

b. Deep wound infection (intra-abdominal abscess).
  i. Occurs usually within the first 30 days posttransplant; bacterial abscesses are diagnosed earlier than fungal abscesses. Of all intra-abdominal infections, about 50% are diffuse and 50% are localized; and about 30% are associated with a leak.
  ii. Clinical presentation: ranges from nonspecific abdominal complaints to diffuse peritonitis, fever, ileus, nausea, vomiting, leukocytosis, hyperglycemia, and sepsis.
  iii. Risk factors: include donor age >45 years, retransplant, pretransplant peritoneal dialysis, graft pancreatitis.
  iv. Diagnosis: abdominal CT with oral and IV contrast (for bladder-drained grafts also with retrograde bladder contrast to rule out leak).
  v. Treatment.
    (a) Percutaneous catheter drainage is appropriate as first-line treatment in stable recipients with localized intra-abdominal abscess.
    (b) For unstable recipients and those with diffuse peritonitis, relaparotomy and open abscess drainage. If leak is present, relaparotomy in enteric-drained recipients is mandatory, but, in selected stable bladder-drained recipients, conservative treatment (prolonged Foley catheterization and percutaneous drainage of localized abscesses) may be attempted.
    (c) IV antibiotics; bowel rest, and nasogastric tube if ileus is present.

4. Leaks.
a. Enteric-drained grafts.
  i. Incidence 5% to 10%.
  ii. Symptoms: abdominal pain, peritonitis, ileus, fever, leukocytosis, or hyperamylasemia.
  iii. Diagnosis.
    (a) Abdominal computed tomography (CT) with oral contrast.
    (b) Diagnosis made at exploratory relaparotomy.
  iv. Treatment: relaparotomy is mandatory (anastomotic revision or transplant pancreatectomy).
b. Bladder-drained grafts.
  i. Incidence: 10% to 15%.
  ii. Early leaks (≤4 weeks posttransplant) usually at the duodenocystostomy anastomosis, late leaks (>4 weeks posttransplant) typically from the graft duodenum (e.g., duodenal ulceration or perforation, CMV infection).
  iii. Symptoms: abdominal pain, distention, fever, vomiting, decreased urine output, peritonitis, improvement after Foley catheter placement. Differential diagnosis must include early ureteral anastomotic leak of a simultaneously transplanted kidney (SPK).
  iv. Diagnosis.
    (a) CT with retrograde bladder contrast (most accurate).
    (b) Low-pressure cystography.
  v. Treatment.

(a) Early leaks: prolonged bladder decompression using Foley catheterization, percutaneous drainage of all intra-abdominal fluid collections.
(b) Infected leaks with peritonitis: relaparotomy and direct leak repair or transplant pancreatectomy.
(c) Late leaks: usually require conversion from bladder to enteric drainage, irrespective of etiology.

5. Graft pancreatitis.
   a. Prolonged posttransplant hyperamylasemia observed in up to 35% of all pancreas transplant recipients.
   b. Risk factors: donor quality (e.g., obesity, age, excessive inotropic requirements), prolonged preservation time (ischemia–reperfusion pancreatitis), pancreatic duct outflow impairment, bladder drainage ("reflux pancreatitis").
   c. Complications: (peri-)pancreatic abscess, pancreatic necrosis (sterile and infected), pancreatic fistula, pseudocyst.
   d. Symptoms: abdominal pain, graft tenderness, nausea, vomiting, ileus. Serum amylase and lipase levels may be elevated but correlate poorly with severity of pancreatitis. Endocrine secretory capacity often is only relatively mildly impaired.
   e. Diagnostic studies: CT with appropriately timed IV contrast bolus to assess pancreatic parenchymal viability and need for débridement of pancreatic necrosis, as well to rule out peripancreatic abscess.
   f. Treatment.
      i. Moderate and severe pancreatitis: nasogastric tube, bowel rest, total parenteral nutrition. Relaparotomy with débridement of pancreatic necrosis as indicated (particularly in recipients with concomitant peripancreatic infection and pancreatic abscess). No definitive data are available on the utility of the somatostatin analog octreotide for prevention and treatment of established pancreatitis.
      ii. Reflux pancreatitis in bladder-drained recipients: insertion of a Foley catheter is not only diagnostic but constitutes also effective treatment. Repetitive episodes of reflux pancreatitis usually require conversion from bladder to enteric drainage.
      iii. Mechanical pancreatic duct obstruction: relaparotomy to address underlying surgical technical problem.

6. Hematuria (bladder-drained recipients).
   a. Early postoperative hematuria: usually anastomotic and self-limited. Severe cases must be treated by continuous bladder irrigation and normalization of coagulation parameters.
   b. Late hematuria: frequently associated with duodenal pathology (e.g., CMV infection). Cystoscopy and graft duodenal segment biopsy may be required. Depending on pathology, conversion to enteric drainage and antiviral treatment may be necessary.

B. Medical complications.

1. Rejection.

a. Acute rejection.

i. Symptoms may include hyperamylasemia, fever, graft tenderness, decreasing urinary amylase; serum creatinine elevation in recipients of a simultaneously transplanted kidney (SPK). Hyperglycemia is a late symptom, usually indicative of an advanced rejection process with irreversible graft injury.

ii. Diagnosis confirmation: percutaneous imaging-guided graft biopsy (gold standard).

iii. Treatment may include:

(a) High-dose IV steroids.

(b) Anti–T-cell therapy.

(c) Plasmapheresis, IV immunoglobulin (IVIG), rituximab, bortezomib, and eculizumab.

b. Chronic rejection.

i. Associated with graft fibrosis and graft vasculopathy; irreversible.

ii. Symptoms: decreasing glucose tolerance, hyperglycemia, increasing HbA1c levels; decreasing or absent urinary amylase (bladder-drained grafts).

iii. Treatment.

(a) Symptomatic: oral antidiabetic agents, return to exogenous insulin therapy.

(b) Pancreas retransplantation.

(c) Graft pancreatectomy is usually not necessary.

2. Acute perioperative myocardial ischemia: diagnosed on postoperative ECG and by elevated troponin and CK-MB levels. Treatment: as in any nontransplant patient.

3. Metabolic complications.

a. Hyperkalemia (in SPK recipients) can occur with delayed kidney graft function and may require IV calcium chloride, insulin, and dextrose, and bicarbonate. Potassium excretion can be augmented by IV loop diuretics; if diuresis cannot be induced, oral sodium polystyrene sulfonate and dialysis may become necessary.

b. Hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia all can occur as the consequence of large-volume diuresis of a simultaneous kidney graft (SPK). Monitor at least every 12 hours; replete electrolytes based on their levels.

c. Hyperglycemia may reflect transient delayed pancreas graft function and may require temporary exogenous insulin.

4. Infectious complications. Most early posttransplant infections are bacterial or fungal. Viral and parasitic infections begin to emerge after 6 weeks posttransplant.

5. Neurologic complications.

a. Seizures. Overall rare; rule out electrolyte abnormalities, acute perioperative cerebrovascular event, drug side effects (e.g., tacrolimus), central nervous system infection (may require lumbar puncture).

b. Acute cerebrovascular events: must be considered in all patients with new onset of seizures or otherwise unexplained postoperatively altered level of consciousness or new onset of other neurologic symptoms.

6. Immunosuppressive drug side effects.
- **a.** Hematologic: leukopenia or thrombocytopenia (e.g., secondary to anti–T-cell therapy with antithymocyte globulin, alemtuzumab; mycophenolate mofetil, sirolimus). Adjust or hold drug doses as necessary.
- **b.** Renal acute nephrotoxicity (calcineurin inhibitors [cyclosporine, tacrolimus]).
- **c.** Neurologic: seizures, tremor, peripheral neuropathic symptoms (calcineurin inhibitors).
- **d.** Pulmonary: pulmonary edema (cytokine release syndrome associated with polyclonal anti–T-cell therapy), interstitial pulmonary fibrosis (sirolimus).
- **e.** Endocrine: hyperglycemia (tacrolimus, steroids).
- **f.** Metabolic: hyperlipidemia associated with steroids, cyclosporine, tacrolimus, and sirolimus.

7. Posttransplant malignancies: posttransplant lymphoproliferative disease; increased incidence of skin cancers.

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136 Critical Care of Liver Transplant Recipients

Nikolaos Chandolias, Vanessa Humphreville, and Ty B. Dunn

I. GENERAL PRINCIPLES

Liver transplantation (LT) has become the treatment of choice for patients with life-threatening liver disorders refractory to other treatments. Depending on the patient's condition and organ availability, options include whole organ or split liver deceased donor, and living donor (partial liver) transplantation. The risks of surgery, recurrent disease, and long-term immunosuppression must be weighed against the potential benefits. Survival rates after LT currently exceed 85% at 1 year and 70% at 5 years.

II. PRETRANSPLANT EVALUATION

A. Indications.

1. Chronic liver disease/cirrhosis.
   - **a.** Most common indications: cirrhosis from hepatitis C virus (HCV), hepatitis B virus (HBV), nonalcoholic steatohepatitis (NASH), alcoholic cirrhosis, primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC).
   - **b.** Signs of advanced and decompensated chronic liver disease include hepatic encephalopathy, refractory ascites and hepatohydrothorax, hepatorenal syndrome, hepatopulmonary syndrome, recurrent and refractory variceal bleeding, recurrent infections (e.g., spontaneous bacterial peritonitis), intractable pruritus, and significant malnutrition (weight loss, muscle wasting).
2. Acute liver failure (ALF)/necrosis.
   - **a.** Classification.
     - **i.** Hyperacute: onset of jaundice to onset of encephalopathy period <7 days.
     - **ii.** Acute: onset of jaundice to onset of encephalopathy period 8 to 28 days.
     - **iii.** Subacute: onset of jaundice to onset of encephalopathy period 5 to 12 weeks; accounts for approximately 5% of all LT in the United States.

b. Etiologies.
  i. Most common etiology: acetaminophen toxicity.
  ii. Other etiologies: infections (hepatitis A, B, E, HSV), metabolic disorders (e.g., Wilson disease), vascular disorders (Budd-Chiari syndrome), autoimmune hepatitis, drug toxicity, and exposure to exogenous toxins.

c. ALF patients may decompensate rapidly; refer early to a transplant center.
  i. Initial presentation: severe hepatic dysfunction, marked coagulopathy, rapid deterioration of mental status, serious metabolic derangements (acidosis), acute renal and respiratory failure.
  ii. Poor prognostic indicators for spontaneous recovery from ALF: factor V level <30%, pH <7.3, international normalized ratio (INR) >6.5, stage 3 or 4 encephalopathy, lack of response to medical therapy within 24 to 48 hours.

2. Other indications.
a. Hepatocellular carcinoma or other tumor confined to the liver.
b. Metabolic liver disease (Ornithine transcarbamylase deficiency, Crigler-Najjar disease, etc.).
c. Congenital (biliary atresia, polycystic liver disease).

B. Contraindications.

1. Extrahepatic tumor.
2. Uncontrolled infection/sepsis.
3. Irreversible neurologic injury.
4. Active alcohol or drug abuse.
5. Contraindication to surgery (usually severe cardiopulmonary disease).

III. INTRAOPERATIVE CARE

A. Venous and arterial monitoring catheters and large-volume infusion lines placed in the operating room can be a source of immediate morbidity (pneumo- or hemothorax, pericardial tamponade, arterial pseudoaneurysm, air embolism).

B. The transplant operation is divided into three phases.

1. Preanhepatic: mobilization of the diseased liver in preparation for its removal.
2. Anhepatic.
a. Characterized by progressive coagulopathy and decreased venous return to the heart secondary to clamping of the inferior vena cava and portal vein.
b. Venovenous and/or portal–venous bypass may be used during this phase to avoid significant hemodynamic changes and decrease bleeding.
c. After the native liver is removed, the donor liver is placed in an orthotopic position, and the vascular (IVC, portal vein, hepatic artery) anastomoses are sewn.

3. Postanhepatic: begins at time of reperfusion.
   a. Reperfusion can lead to hypotension, pulmonary hypertension, and arrhythmias.
   b. Hemodynamic changes may result from acidosis, electrolyte abnormalities (mainly hyperkalemia), air embolus, or volume overload.
   c. Close monitoring, appropriate volume resuscitation, and electrolyte management are critical.
   d. Hemostasis and completion of the biliary anastomosis are done.

IV. POSTOPERATIVE CONSIDERATIONS

A. Postoperative course depends largely on the patient's preoperative status and the development of any complications. Basic care of all patients involves the following.

1. Stabilization and recovery of the major organ systems.
2. Monitoring for evidence of improving graft function: improving mental status and coagulation profile, resolution of hypoglycemia, clearance of serum lactate, and decreasing transaminases and bilirubin (48 to 72 hours).
3. Provision of adequate immunosuppression.
4. Avoidance of common pitfalls: oversedation with benzodiazepines and narcotics, unaddressed hypotension (systolic blood pressure <100 mm Hg) that may contribute to renal dysfunction and graft thrombosis, and too rapid correction of preexisting hyponatremia, which may lead to demyelinating syndromes.
5. Vigilant surveillance and management of early complications (see subsequent text).

B. Surgical issues.

1. Hemorrhage.
   a. Postoperative bleeding is common; it can be exacerbated by coagulopathy, fibrinolysis, thrombocytopenia, and platelet dysfunction.
   b. Signs of ongoing blood loss: hypotension, tachycardia, decreasing cardiac filling pressures, falling hemoglobin, and increasing surgical drain output.
   c. Surgical exploration is indicated if bleeding persists despite correction of coagulation deficiencies.
2. Vascular complications.
   a. Overall incidence: 8% to 12%.
   b. Thrombosis is the most common early event; stenosis and pseudoaneurysm formation occur later.
   c. Doppler ultrasound evaluation is the initial imaging study of choice.
   d. Hepatic artery thrombosis (HAT).
      i. Incidence: approximately 2% in adults and 10% in children.
      ii. Detected early; up to 50% of grafts can be salvaged with urgent exploration, thrombectomy, or revision of the anastomosis.
      iii. Approximately 50% of patients with HAT require retransplantation.
      iv. Can also present less acutely with bile duct ischemia resulting in anastomotic bile leak or diffuse intrahepatic small duct strictures/bilomas.

- **e.** Thrombosis of portal vein or hepatic veins, or stenosis of suprahepatic inferior vena cava anastomosis.
  - **i.** Less common than HAT.
  - **ii.** May be heralded by liver dysfunction, tense ascites, or variceal bleeding.
  - **iii.** If diagnosed early, operative thrombectomy, revision of the anastomosis (e.g., for portal vein thrombosis), or endovascular stenting (e.g., for suprahepatic anastomotic caval stenosis) may be successful.
  - **iv.** Late portal vein thrombosis: liver function is frequently preserved because of collateral veins; retransplantation is usually not necessary; and attention is directed to treatment of portal hypertension.

3. Biliary complications.
- **a.** Incidence: 15% to 35%. Rate higher for partial graft recipients, largely due to cut surface leaks; up to 60% in donation after cardiac death (DCD) graft recipients.
- **b.** Bile leaks.
  - **i.** Typically occur early posttransplant.
  - **ii.** Clinical features: fever, abdominal pain, leukocytosis, elevated bilirubin.
  - **iii.** Diagnosis: computed tomography (CT) or ultrasound may demonstrate a fluid collection, but confirmation of active leak requires hepatoiminodiacetic acid (HIDA) scintigram or cholangiography.
  - **iv.** Management: drainage and endoscopic stent placement; operative repair if unsuccessful.
- **c.** Strictures.
  - **i.** Usually anastomotic, likely related to local ischemia.
  - **ii.** Clinical features: cholestasis, cholangitis.
  - **iii.** Diagnosis: ultrasound, magnetic resonance cholangiopancreatography, cholangiography.
  - **iv.** Management: balloon dilatation and stent placement across the stricture; surgical revision reserved for endoscopic failures. Diffuse ischemic-type intrahepatic biliary strictures frequently require retransplantation.

4. Wound complications.
- **a.** Infection, hematoma, and seroma (early posttransplant).
  - **i.** Diagnosis: drainage, increasing pain, erythema, fluctuance.
  - **ii.** Management: open wound, perform serial dressing changes, healing by secondary intention. If significant cellulitis or systemic symptoms, intravenous antibiotics are indicated.
- **b.** Incisional hernias.
  - **i.** Associated with malnutrition, attenuated fascia, and immunosuppression.
  - **ii.** Often require surgical repair, particularly if symptomatic.

5. Primary nonfunction (PNF).
   a. Transplanted graft is incapable of performing vital synthetic and metabolic functions; recipient must be retransplanted or risks death within the first week.
   b. Incidence: approximately 3% to 5% in the current era.
   c. Donor risk factors: donor age >50, macrosteatosis >30%, donor ICU stay >3 days, cold ischemia time >12 hours, DCD donor, and split liver graft.
   d. Diagnosis: by exclusion. Must rule out HAT, accelerated acute rejection, sepsis.
   e. Treatment options: IV prostaglandin E_1 (not supported by compelling evidence); early listing for retransplantation (the only available definitive treatment).

C. Nonsurgical issues.

1. Neurologic: often related to degree of preoperative encephalopathy, history of substance abuse, uremia, calcineurin inhibitor side effects, metabolic derangements, or a poorly functioning graft.
   a. Clinical findings: persistently decreased level of consciousness, seizures, and focal neurologic deficits.
   b. Early Imaging: CT or MRI to rule out specific diagnoses: ischemic encephalopathy, intracranial hemorrhage, central pontine myelinolysis, or posterior reversible encephalopathy syndrome (PRES).
   c. EEG: rule out status epilepticus.
   d. Avoid benzodiazepines; consider antipsychotic drugs (haloperidol, risperidone).
2. Cardiovascular: a hyperdynamic state characterized by high cardiac output and low systemic vascular resistance is frequently observed.
   a. Likely related to alterations in nitric oxide metabolism; generally improves over time after transplant.
   b. Swan-Ganz catheters or TEE for hemodynamic monitoring in the ICU.
3. Pulmonary: dysfunction can be preexisting or *de novo*. Early extubation protocols reduce ICU and hospital length of stay. Common problems are the following:
   a. Atelectasis: may result from incisional pain, hepatohydrothorax or mucus plugs. Treatment is aimed at underlying cause(s).
   b. Pulmonary edema and pleural effusions: exacerbated by massive blood transfusions or hypoalbuminemia. Treatment: careful fluid administration and judicious use of diuretics. Percutaneous drainage of moderate/large collections.
   c. Hepatopulmonary syndrome: associated with hypoxia, intrapulmonary shunts, and often normal pulmonary artery pressures; typically improves after LT.
   d. Portopulmonary hypertension: pulmonary hypertension that arises in the setting of severe liver disease. Mean pulmonary artery pressure >35 mm Hg on preoperative cardiac echo considered prohibitive for transplant. Vasodilators (epoprostenol), inhaled nitric oxide, and restrictive fluid management may be necessary to prevent right ventricular overload and subsequent hepatic congestion with graft dysfunction.

e. Acute respiratory distress syndrome (ARDS).
  i. Low incidence, but high mortality.
  ii. Protective ventilation strategy to prevent barotrauma may reduce mortality.
f. Respiratory infections.
  i. Nosocomial and ventilator-associated pneumonias caused by typical microorganisms in the early postoperative phase.
  ii. Opportunistic organisms, resistant bacteria, and fungal infections predominate later in the course, but also may occur after a long preoperative ICU stay or during periods of increased immunosuppression.

4. Renal: renal dysfunction is common in liver recipients and associated with increased perioperative mortality. Causes of renal failure.
a. Pretransplant: hepatorenal syndrome, acute tubular necrosis, and medical comorbidity (diabetes).
b. Posttransplant: hypovolemia, ischemic acute tubular necrosis (early); drug nephrotoxicity due to calcineurin inhibitors (early and late).

5. Immunosuppression complications: include posttransplant diabetes, hyperlipidemia, opportunistic viral and fungal infections, increased incidence of squamous and basal cell skin cancers, and posttransplant lymphoproliferative disease.

6. Recurrence of primary liver disease may require treatment and can significantly impact graft and patient survival.
a. Hepatitis B: highly effective peri- and posttransplant prophylactic protocols that include hepatitis B immunoglobulin and/or nucleoside analogs (e.g., lamivudine, adefovir, entecavir) have significantly lowered recurrence rates.
b. Hepatitis C: approximately 20% to 30% recurrent cirrhosis at 5 years posttransplant; well-tolerated routine pharmacoprophylaxis not available; data are emerging regarding the efficacy and safety of triple therapy posttransplant.
c. Autoimmune liver diseases (including autoimmune hepatitis, PBC, PSC).
  i. Low rates of clinically significant recurrence.
  ii. Potential but unproven benefit of long-term posttransplant maintenance on steroids.

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137 Critical Care of Heart and Heart–Lung Transplant Recipients

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HEART TRANSPLANT RECIPIENTS

I. GENERAL PRINCIPLES

A. Cardiac transplant patients are similar to nontransplant cardiac surgery patients in many regards, but there are several key differences that are due in part to the denervation of the transplanted heart.

1. Autonomic interventions are often futile.
   - **a.** Atropine.
   - **b.** Maneuvers.
     - **i.** Carotid sinus massage.
     - **ii.** Valsalva.
2. Intrinsic SA node will pace between 90 and 110 bpm. Changes in HR are mediated via circulating catecholamines (epinephrine) rather than nervous innervation, so the response is slower.
3. Pain: Patients may not experience cardiac chest pain.

B. Posttransplant monitoring is similar to that in nontransplant cardiac surgery patients.

1. Hemodynamics: arterial line, central venous line, pulse oximetry: these lines aid in determining cardiac output, need for IV fluids/inotropic support, treatment of pulmonary hypertension, and need for further interventions.
2. Epicardial pacing wires (placed intraoperatively, backup rate = 60 bpm). Cardiac rhythm support, used in the treatment of posttransplant bradycardia.
3. Mediastinal and pleural chest tubes are placed to −20 cm H_2O suction.
   - **a.** To monitor for postoperative intrathoracic hemorrhage.
   - **b.** Prevention of cardiac tamponade.
4. Foley catheter.
   - **a.** To monitor urine output.
   - **b.** To assess core body temperature.

II. POSTOPERATIVE CONSIDERATIONS

A. Immediately posttransplant, the focus is on achieving and maintaining hemodynamic stability.

B. Volume status: IV fluids (crystalloids or colloids) to maintain adequate systemic perfusion as evidenced by the following.

1. Palpable distal pulses, upper extremities.
2. Urine output >0.5 mL/kg/h (without diuretics).
3. Acid–base balance.
4. Cardiac index >2.0 L/min/m^2.
5. CVP of 8 to 12 cm H_2O and/or pulmonary capillary wedge pressure of 15 to 20 mm Hg.

C. Hemodynamics.

1. Inotropic support (required when above criteria are not met; β-adrenergic agents should be used in the presence of adequate preload).
2. Afterload management goals: mean arterial pressure (MAP) 65 to 80 mm Hg and/or a calculated systemic vascular resistance 1,000 to 1,400 dynes/s/cm^5. MAPs > 80 mm Hg should be treated in order to avoid excessive ventricular wall stress.
   a. IV sodium nitroprusside.
   b. IV nitroglycerin (associated with less intrapulmonary shunting than sodium nitroprusside due to relative preservation of the pulmonary hypoxic vasoconstrictor reflex).

D. Respiratory management: follows the same principles as after routine cardiac surgery.

E. Electrolyte balance and renal function: follows the same principles as after routine cardiac surgery.

1. Serum electrolytes are closely monitored. Maintaining normal K^+, Mg^{2+}, and Ca^{2+} levels is particularly important in reducing the frequency of arrhythmias.
2. On initiation of immunosuppressant therapies, particularly cyclosporine, serum creatinine is followed closely to monitor for early nephrotoxicity.
3. Diuresis with furosemide is usually initiated 24 to 48 hours postoperatively and continued to achieve euvolemia.

F. Perioperative infection prophylaxis.

1. General prophylaxis: First-generation cephalosporins (vancomycin for patients with β-lactam allergy) are administered 30 minutes prior to induction of anesthesia and continued for 48 hours postoperatively.
2. Prophylaxis for *Pneumocystis jirovecii* pneumonia, *Toxoplasma gondii*, *Listeria*, *Legionella*, and *Nocardia*: Trimethoprim–sulfamethoxazole (TMP-SMX) (or aerosolized pentamidine if TMP-SMX is not tolerated).
3. Prophylaxis for prevention of mucocutaneous candidiasis.
   a. Nystatin or clotrimazole.
   b. Fluconazole is indicated for patients with a history of candidiasis refractory to these topical antifungal agents or involving the esophagus.
4. Prophylaxis for herpes simplex and varicella zoster viruses: low-dose acyclovir.

5. Latent tuberculosis infection: recipients with a positive purified protein derivative skin test should be considered for prophylaxis with isoniazid or rifampin.
6. Cytomegalovirus (CMV) infection: CMV is the most common cause of infection in cardiac transplant recipients and may play a role in chronic allograft rejection. Routine prophylaxis with IV ganciclovir for 1 to 2 weeks followed by universal prophylaxis with oral valganciclovir for 3 months is recommended, particularly for the high-risk CMV-seropositive donor/seronegative recipient combinations.
7. *Aspergillus* prophylaxis.
   a. Air filtration for all cardiac transplant recipients.
   b. High-risk patients, including those with isolated *Aspergillus* species in respiratory tract cultures, may additionally benefit from itraconazole (400 mg daily administered orally starting on day 5 after transplantation for 3 to 6 months).

G. Dysrhythmias.

1. Bradycardia: sinus or junctional bradycardia occurs in >50% of heart transplant recipients.
   a. Therapeutic goal is to achieve heart rate of 90 to 110 bpm.
      i. Inotropic agents.
      ii. Chronotropic agents.
      iii. Epicardial pacing.
      iv. Temporary pacemaker.
   b. Refractory bradycardia: in rare cases of persistent bradycardia, permanent pacemakers may be required.
2. Atrial fibrillation/flutter.
   a. Digoxin: Cardiac allografts require higher doses than innervated hearts.
   b. May indicate acute allograft rejection.
3. Ventricular arrhythmias occur in up to 60% of transplant recipients and include premature ventricular contractions and nonsustained ventricular tachycardia. Underlying etiologies should be aggressively discerned (e.g., acute rejection, electrolyte disturbances, acidosis).

H. Coagulopathy.

1. Predisposing factors.
   a. Preoperative warfarin therapy.
   b. Cardiopulmonary bypass.
   c. Hepatic failure.
   d. Chronic renal insufficiency.
2. Monitoring with postoperative labs: prothrombin time or INR, partial thromboplastin time, platelet count, and fibrinogen levels.
3. Correction as indicated with fresh frozen plasma (FFP), platelets, cryoprecipitate, and/or protamine.

III. IMMUNOSUPPRESSION

A. The primary objective of immunosuppressive therapy is to balance immunosuppression and immunocompetence while minimizing toxicity associated with immunotherapy.

1. Selective modulation of the immune response to prevent allograft rejection.
2. Maintenance of the immune response to prevent infection and neoplasia.

B. The choice and combinations of immunosuppressive agents, doses, and schedules vary significantly among transplantation centers. Data from the 2007 report of the Registry of the International Society for Heart and Lung Transplantation suggest that there is no consensus on immunosuppression therapy regimens. Regimens are individualized by transplant program.

C. Multidrug regimens are designed to exploit synergism between the different mechanisms of action, permitting lower doses of each component and reduced toxicities.

D. Most centers use triple immunosuppressive therapy consisting of cyclosporine or tacrolimus, corticosteroids, and azathioprine or mycophenolate mofetil.

IV. EARLY ALLOGRAFT FAILURE

A. Accounts for up to 25% of perioperative deaths.

B. The most common etiologies include the following.

1. Pulmonary hypertension.
2. Myocardial injury due to prolonged ischemia or inadequate preservation.
3. Acute rejection.

C. Right ventricular failure is a leading cause of early mortality.

1. Echocardiographic findings.
   - **a.** Hypokinetic, dilated right ventricle.
   - **b.** Inadequate left ventricular filling.
   - **c.** Elevated central venous pressures (15 to 25 mm H_2O).
   - **d.** Decreased cardiac output.
2. Initial management.
   - **a.** Pulmonary vasodilators: Inhaled nitric oxide, nitroglycerin, milrinone, prostaglandin E1, inhaled iloprost.
   - **b.** Refractory pulmonary hypertension may require a temporary right ventricular assist device.

D. Left ventricular failure is less frequently encountered than right ventricular failure.

1. Echocardiographic findings.
   - **a.** Hypokinetic, dilated left ventricle.
   - **b.** Elevated left ventricular end-diastolic pressures.
   - **c.** Decreased cardiac output.
   - **d.** Systemic hypotension.
2. Initial management.
   - **a.** IV inotropic support: epinephrine, dobutamine, dopamine, milrinone.
   - **b.** Afterload reduction: nitroprusside, milrinone.
   - **c.** Preload management: Avoid fluid overload.
3. Refractory left ventricular failure may require a temporary intra-aortic balloon pump or left ventricular assist device.

HEART–LUNG TRANSPLANT RECIPIENTS

I. GENERAL PRINCIPLES

A. The primary objectives of early postoperative care are to maintain adequate perfusion and gas exchange while minimizing IV fluids, cardiac work, and barotrauma.

B. The transplanted lung is denervated: patients require aggressive pulmonary toilet postoperatively because of

1. Diminished cough reflex.
2. Impaired mucociliary clearance.

C. Early pulmonary allograft function is impacted by ischemia, reperfusion injury, and disrupted pulmonary lymphatics, which can lead to the following.

1. Increased vascular permeability.
2. Interstitial edema.
3. Elevated alveolar–arterial gradient.

II. POSTOPERATIVE MANAGEMENT

A. Inotropic and fluid management (see above, as for Heart Transplant Recipients).

B. Monitoring: As for heart transplant recipients, plus pulmonary artery catheter. This is essential when the recipient has known pulmonary hypertension and the donor has right ventricular dysfunction.

C. Respiratory management.

1. Immediately postoperatively.
a. Anteroposterior chest radiograph.
b. Ventilator set to minimize barotrauma, which may compromise bronchial mucosal blood flow.
c. Frequent arterial blood gases.
d. Postextubation pulmonary management includes diuresis, supplemental oxygen as needed, bronchodilators, aggressive pulmonary toilet and incentive spirometry, and frequent-interval chest radiographs.
e. Inhalation therapy with albuterol and ipratropium bromide is helpful in cases of bronchospasm in the native lung due to underlying disease, and/or in the lung allograft due to mild ischemia–reperfusion injury.
f. Due to pulmonary airway denervation, pulmonary toilet with frequent endotracheal suctioning is necessary to avoid mucous plugs and atelectasis. Care should be taken during deep suctioning to avoid unnecessary trauma to the tracheal or bronchial anastomoses.

D. Coagulopathy (see above, as for Heart Transplant Recipients).

E. Electrolyte and renal dysfunction (see above, as for Heart Transplant Recipients).

F. Perioperative infection prophylaxis (see above, as for Heart Transplant Recipients).

G. Immunosuppression (see above, as for Heart Transplant Recipients).

III. EARLY ALLOGRAFT DYSFUNCTION AND FAILURE

A. Cardiac allograft dysfunction and dysrhythmias in heart–lung recipients are managed as in heart transplant recipients (see sections II E and G above).

B. Lung allograft dysfunction.

1. Early lung allograft dysfunction manifests as persistently marginal gas exchange and pulmonary hypertension in the absence of infection or rejection.
2. Particularly severe cases of pulmonary hypertension can lead to right ventricular failure.
3. Early lung allograft dysfunction is managed by increasing FIO_2, PEEP, sedation, neuromuscular blockade, and careful diuresis to maintain fluid balance and reduce pulmonary edema.
4. In cases of persistently severe graft dysfunction refractory to standard ventilatory and medical management, extracorporeal membrane oxygenation (ECMO) and inhaled nitric oxide may be used to stabilize gas exchange.
   - **a.** Nitric oxide relaxes preconstricted pulmonary vascular smooth muscle and is justified early postoperatively in recipients with pulmonary infiltrates, poor oxygenation, and mild-to-moderate pulmonary hypertension.
   - **b.** Right heart failure, manifested by a rise in CVP and fall in cardiac output, is monitored during nitric oxide weaning.

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138 Critical Care of Hematopoietic Cell Transplant Recipients

Marco Mielcarek

I. GENERAL PRINCIPLES

A. Definition.

1. Hematopoietic cell transplantation (HCT) is a potentially curative treatment for malignant and nonmalignant diseases including leukemia, lymphoma, multiple myeloma, aplastic anemia, hemoglobinopathies, and congenital immune deficiencies.
2. Chemoradiation is used to eradicate the underlying disease and is followed by intravenous infusion of the stem cell graft.
3. Among other cells, the graft contains the stem cells that reconstitute the ablated hematopoietic system.
4. Immunosuppressive therapy is required after allogeneic HCT to prevent graft-versus-host-disease (GVHD) and graft rejection.

B. Classification: the type of HCT used is a complex decision based on patient's age, diagnosis, donor availability, and comorbidity.

1. Stem cell source.
   a. Bone marrow.
   b. "Mobilized" peripheral blood: growth factors are used alone (e.g., granulocyte-colony stimulating factor [G-CSF]) or in combination with chemotherapy (in autologous HCT) for "mobilization" of hematopoietic stem cells, which are collected by leukapheresis.
   c. Cord blood: collected from the umbilical cord after delivery and cryopreserved.
2. Donor type.
   a. Autologous: using one's own stem cells.
   b. Syngeneic: identical twin (no genetic donor/recipient disparity).
   c. Allogeneic: donor with similar human leukocyte antigen (HLA) type.
      i. Sibling donor: Statistical likelihood for an HLA-identical sibling is 25% per sibling.
      ii. Unrelated donor: HLA-matched volunteer donor is identified through a database search.
3. Intensity of the preparative regimen.
   a. Myeloablative: the regimen ablates the hematopoietic system and leads to transient but profound myelosuppression with pancytopenia.
   b. Reduced-intensity: preparative regimen has reduced early toxicity and may therefore be outpatient based. The burden of disease

eradication is on ensuing immunologic graft-versus-tumor effects. Onset of typical post-HCT complications, such as GVHD and infections, may be delayed.

C. Transplant statistics: estimated number of HCTs: 45,000 to 50,000/year worldwide (approximately two-thirds autologous and one-third allogeneic HCTs).

D. Risk factors for posttransplant complications: age, intensity of the preparative regimen, type and stage of underlying disease, presence of comorbidities, and HLA-disparity between donor and recipient. Allogeneic HCT recipients have greater risk of transplant-related morbidity and mortality than autologous recipients.

E. Prognosis: highly variable and influenced by numerous risk factors related to the transplant procedure and to recurrent malignancy after surviving the transplant.

II. TRANSPLANT-RELATED COMPLICATIONS

A. HCT-related morbidity and mortality can be categorized into four groups (Fig. 138-1).

1. Toxicity of the preparative regimen.
2. Infection.
3. Bleeding.
4. GVHD.

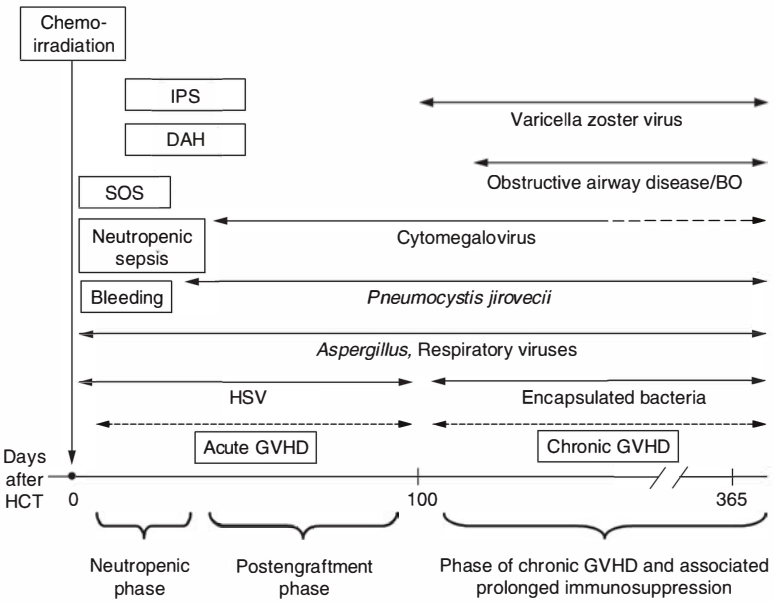

Figure 138-1. Complications after myeloablative allogeneic HCT. IPS, idiopathic pneumonia syndrome; DAH, diffuse alveolar hemorrhage; SOS, sinusoidal obstruction syndrome; BO, bronchiolitis obliterans; HSV, herpes simplex virus; RSV, respiratory syncytial virus; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant.

III. TOXICITY OF THE PREPARATIVE REGIMEN

A. General principles: cytotoxic chemotherapy with or without total body irradiation (TBI) may compromise the function of many organs. This toxicity occurs predominantly within the first 3 to 4 weeks of HCT and is less severe after reduced-intensity HCT.

1. Lung.

a. Etiology/pathophysiology.

i. Idiopathic pneumonia syndrome (IPS), a noninfectious inflammatory lung process that may be triggered by TBI and chemotherapeutic drugs (e.g., carmustine [BCNU], busulfan); median onset: 2 to 3 weeks after HCT. Contributing factors include release of inflammatory cytokines due to alloreactivity or sepsis; role of latent infections is controversial.

ii. Other common noninfectious pulmonary problems that may occur within 30 days posttransplant include diffuse alveolar hemorrhage (DAH), edema syndromes due to fluid overload or cyclophosphamide-induced cardiomyopathy, and sepsis with adult respiratory distress syndrome (ARDS).

b. Diagnosis.

i. Clinical presentation: fever, nonproductive cough, tachypnea, hypoxemia. Hemoptysis is an infrequent symptom of IPS or DAH.

ii. Laboratory and radiologic studies: diffuse or multifocal intraalveolar or interstitial infiltrates on chest radiography or computed tomography (CT). An increased alveolar–arterial oxygen gradient, a new restrictive pattern, or a diffusion-capacity abnormality is evidence for abnormal pulmonary physiology. Echocardiography may be useful to rule out cardiogenic pulmonary edema.

iii. Differential diagnosis: must distinguish noninfectious (IPS) from infectious causes (e.g., cytomegalovirus [CMV], bacterial, fungal) of diffuse pulmonary infiltrates. Localized parenchymal lung disease is usually due to infection. Diagnosis of IPS requires a negative bronchoalveolar lavage or lung biopsy with stains and cultures for bacteria, fungi, and viruses. Bronchiolitis obliterans (BO) can be related to chronic GVHD. Patients may also have pulmonary relapse of their underlying malignancy.

iv. Treatment: IPS treatment consists of supportive care, secondary infection prevention, empiric broad-spectrum antibiotics, and trial of diuretics. Bleeding disorders should be corrected. Although there are no prospective trials to support the use of high-dose corticosteroids, a small percentage of IPS patients respond to prednisone (1 to 2 mg/kg/d). Patients with BO frequently respond to corticosteroid therapy (1 mg/kg/d).

v. Prognosis: mortality of diffuse IPS after myeloablative HCT is 50% to 70%. Approximately 6% of patients who require mechanical ventilation after HCT survive for 30 days after extubation and are discharged; half of these survivors live for >2 years. The presence of either hemodynamic instability or sustained hepatic and renal failure further worsens their prognosis. Since

ongoing improvements in supportive care may improve outcome, treatment decisions have to be individualized. Therefore, aggressive management, including mechanical ventilation, to identify and treat *reversible* causes of respiratory failure is a reasonable initial approach for most HCT recipients with diffuse or multifocal pulmonary infiltrates.

2. Gastrointestinal (GI) tract.
   a. Etiology/pathophysiology: oral mucositis, esophagitis/gastritis, and diarrhea are commonly associated with chemoradiation and can be worsened by methotrexate given for GVHD prophylaxis. Mucositis places patients at high risk for aspiration and facilitates translocation of intestinal bacteria and sepsis.
   b. Diagnosis.
      i. Clinical presentation: dysphagia, odynophagia, mucosal ulcerations and hemorrhage, oropharyngeal hypersecretion, anorexia, nausea, vomiting, diarrhea, dyspnea, or signs of upper airway compromise.
      ii. Laboratory and radiologic studies: usually noncontributory.
      iii. Differential diagnosis: mucositis may be associated with infection (herpes simplex virus [HSV], CMV, varicella zoster virus [VZV], or fungal) and GVHD. Anorexia, nausea, vomiting, and diarrhea persisting beyond 3 weeks after allogeneic HCT may be caused by GVHD and/or herpes virus infection, or medications.
   c. Treatment: supportive care, opioid analgesia, institution of parenteral nutrition. Severe oropharyngeal mucositis with impending airway compromise may require intubation for airway protection.
3. Liver.
   a. Etiology/pathophysiology: jaundice, hepatomegaly, and abnormal liver tests within the first 2 months of HCT may have many causes including toxicity from the preparative regimen. Total bilirubin >4 mg/dL, regardless of etiology, is a powerful predictor for transplant-related mortality. Sinusoidal obstruction syndrome (SOS) occurs in up to 50% of myeloablated HCT recipients. Cyclophosphamide, TBI, and preexisting chronic liver disease are risk factors for SOS.
   b. Diagnosis.
      i. Clinical presentation: tender hepatomegaly, renal sodium retention with weight gain, and jaundice following the preparative regimen in the absence of other explanations for these signs and symptoms are suggestive of SOS.
      ii. Laboratory and radiologic studies: total serum bilirubin sensitive but nonspecific. Hepatomegaly, ascites, and attenuated hepatic venous flow by ultrasound and venous duplex Doppler imaging are consistent with SOS; biliary dilatation or infiltrative lesions must be excluded. Measurement of the hepatic venous pressure gradient and biopsy may be indicated.
      iii. Differential diagnosis: other causes of post-HCT jaundice seldom lead to renal sodium avidity, rapid weight gain, and hepatomegaly before the onset of jaundice. Combinations of illnesses

that may mimic SOS are sepsis with renal insufficiency and cholestasis, cholestatic liver disease with hemolysis and congestive heart failure, and GVHD and sepsis syndrome. Hepatic VZV infection may occur in VZV-seropositive patients who are not on prophylactic acyclovir (transaminases typically >1,000 units/mL). Empiric acyclovir should be given until VZV hepatitis has been ruled out.

c. Treatment: ursodeoxycholic acid has reduced severity of post-HCT SOS in two randomized trials. As 70% to 85% of patients recover spontaneously, supportive management of sodium and water balance for symptomatic ascites or pulmonary compromise is important. Uncontrolled trials with defibrotide have been promising.

4. Heart.

a. Etiology/pathophysiology: the major dose-limiting toxicity of high-dose cyclophosphamide (doses above 200 mg/kg), a component of many preparative regimens, is cardiac injury with hemorrhagic myocardial necrosis. Patients who did receive a cumulative dose of the anthracycline doxorubicin of >550 mg/m^2 are at increased risk for developing heart failure.

b. Diagnosis.

i. Clinical presentation: congestive heart failure occurring within a few days of receiving cyclophosphamide. Onset of anthracycline-related cardiomyopathy may be delayed.

ii. Laboratory and radiologic studies: voltage loss on electrocardiogram (ECG); arrhythmia; echocardiogram shows signs of systolic dysfunction. Pericardial effusion/tamponade may be present.

iii. Differential diagnosis: congestive heart failure from fluid overload, malignant effusion, and infectious perimyocarditis.

c. Treatment: management of fluid and sodium balance, afterload reduction, inotropes.

5. Kidney.

a. Etiology/pathophysiology: drugs that most commonly affect renal function in transplant patients are cyclosporine, tacrolimus, amphotericin, and aminoglycosides. Six to ten percent of allogeneic HCT recipients develop a thrombotic microangiopathy (TMA), which is the result of endothelial injury by chemoradiation, cyclosporine, or tacrolimus. Overall mortality of acute renal failure post-HCT requiring dialysis exceeds 80%.

b. Diagnosis.

i. Clinical presentation: patients with drug-related renal dysfunction are typically asymptomatic. Classical symptoms associated with thrombotic thrombocytopenic purpura (TTP) (thrombocytopenia, fragmentation hemolysis, neurologic abnormalities, and fever) may not be present in HCT patients with TMA.

ii. Laboratory studies: serum creatinine elevation. Cyclosporine and amphotericin may lead to renal potassium and magnesium wasting. The hallmark of TMA is red blood cell (RBC) fragmentation (schistocytosis) associated with increased RBC turnover (reticulocytosis,

elevation of lactate dehydrogenase [LDH], and indirect bilirubin levels), without evidence for either immune-mediated hemolysis or disseminated intravascular coagulation (DIC).

iii. Differential diagnosis: liver disease (SOS) may cause renal dysfunction (hepatorenal syndrome) with increased renal sodium avidity. Consider also prerenal mechanisms (heart failure, hypotension, volume depletion), sepsis, and tumor lysis syndrome.

c. Treatment: discontinuation of the likely offending agent; adjustment of cyclosporine/tacrolimus blood levels; optimization of intravascular volume status. Efficacy of substituting tacrolimus for cyclosporine is controversial. In contrast to classic TTP, TMA after HCT is usually not responsive to plasma exchange.

6. Central nervous system (CNS).

a. Etiology/pathophysiology: neurologic complications after HCT can have infectious, metabolic, toxic, immune-mediated, and cerebrovascular causes. Their timing after HCT may aid with the differential diagnosis.

i. During or shortly after conditioning therapy: chemotherapeutic drugs such as high-dose busulfan and BCNU may cause encephalopathy and seizures (importance of prophylactic anticonvulsant treatment). CNS toxicity manifesting as coma has been reported with ifosfamide. High-dose cytarabine may cause cerebellar dysfunction, encephalopathy, and seizures.

ii. Pre-engraftment (during pancytopenia): intracranial hemorrhage is a frequently fatal complication in patients with refractory thrombocytopenia. Subdural hematomas have a more favorable prognosis. Encephalopathy is most often related to gram-negative sepsis, the use of sedative–hypnotic drugs, and hepatic dysfunction due to SOS. Bacterial meningitis is rare. Human herpes virus 6 (HHV-6) encephalitis may typically be encountered during the first 30 days after HCT.

iii. Postengraftment (during GVHD-related immunosuppression): post-HCT immunosuppression increases the risk of opportunistic infections. *Aspergillus* spp. account for 30% to 50% of CNS infections in autopsy series. Given the available prophylaxis with trimethoprim–sulfamethoxazole and acyclovir, *Toxoplasma gondii*, HSV, and VZV encephalitis are rarely seen in HCT recipients. Cyclosporine causes more neurologic problems (seizures, encephalopathy) in HCT patients than any other drug. Corticosteroids may be associated with psychosis, mania, or delirium.

b. Diagnosis.

i. Clinical presentation: focal symptoms are more suggestive of infectious or cerebrovascular etiologies; diffuse symptoms (delirium, coma) may have metabolic causes. CNS infections can present without fever.

ii. Laboratory and radiologic studies: a thorough workup should include magnetic resonance imaging (MRI) or CT, followed by lumbar puncture for CSF analysis (cultures, stains, and viral

[HHV-6] polymerase chain reaction [PCR] studies) for suspected infection. Patients with calcineurin-inhibitor neurotoxicity may have MRI changes, most often in the occipital lobe white matter.

c. Treatment: post-HCT CNS infections have a poor prognosis. Treatment of metabolic encephalopathy should be directed at the underlying problem; discontinue offending drugs. Calcineurin-inhibitor neurotoxicity: Discontinue cyclosporine or tacrolimus temporarily, restart at a lower dose, or switch the drug.

IV. INFECTION

A. General principles: infections are frequent after autologous and allogeneic HCT. Occurrence pattern is determined by several factors including pretransplant history, intensity of the preparative regimen, regimen used for infection prevention, microbiological flora of the patient and the individual transplant unit, and degree of immunosuppression after transplant (GVHD activity). Recovery after HCT can be divided broadly into three phases with typical infection patterns.

1. Pre-engraftment (<30 days posttransplant): characterized by neutropenia and oral/GI mucosal injury. Bacterial and fungal infections are most common. Hence, many transplant centers use a prophylactic antibiotic regimen. Viral infections are most commonly caused by HSV. With indwelling central venous catheters, the risk for infections caused by gram-positive organisms (e.g., staphylococci and streptococci) increases. Fungal infections during this period may present with skin lesions (*Candida* spp.), sinus involvement (*Aspergillus* spp. and Mucor), lung lesions (*Aspergillus* spp.), or hepatitis (*Candida* spp.).

a. Workup and treatment: see Chapter 67 *Infections in Immunocompromised Hosts*.

2. Postengraftment (30 to 100 days posttransplant). Characterized by skin and mucosal injury, and compromised cellular immunity related to GVHD and its treatment. Viral (CMV) and fungal (*Aspergillus* spp., *Pneumocystis jirovecii*) infections predominate. Gram-negative bacteremic episodes may be related to GVHD-associated mucosal injury, and gram-positive infections may occur due to indwelling catheters. Other causes of fever after engraftment include occult sinusitis, hepatosplenic candidiasis, and pulmonary or disseminated *Aspergillus* infection.

a. Workup and treatment: see Chapter 67 *Infections in Immunocompromised Hosts*.

3. Late phase (>100 days posttransplant). Patients with chronic GVHD have persistently decreased cellular immunity. They are highly susceptible to recurrent bacterial infections, especially from encapsulated bacteria, including *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* (functional asplenia). Nonbacterial infections at this stage are commonly caused by VZV, CMV, *P. jirovecii*, and *Aspergillus* spp.

a. Workup and treatment: See Chapter 67 *Infections in Immunocompromised Hosts*.

V. BLEEDING

A. Etiology/pathophysiology: bleeding can occur as a result of thrombocytopenia or coagulopathy. Breakdown of mucosal barriers (regimen-related toxicity and/or GVHD) increases likelihood of hemorrhage. CNS hemorrhage can be rapidly fatal. Hemorrhagic cystitis can be caused by high-dose cyclophosphamide and BK virus infection.

B. Diagnosis: depends on presentation—endoscopic evaluation (colonoscopy, esophagogastroduodenoscopy [EGD], bronchoscopy) or CNS imaging.

C. Treatment: platelet count <10,000/mm^3 increases the risk for spontaneous bleeding and should be treated prophylactically with platelet transfusion. The decision to transfuse platelets for platelet counts >10,000/mm^3 should be guided by the clinical situation. All transplant patients should receive either CMV-negative or leukocyte-reduced (leukocytes harbor CMV), and irradiated (to prevent transfusion-associated GVHD) blood products. DAH may manifest with pulmonary infiltrates, and bleeding can be seen on bronchoscopy; treatment: high-dose corticosteroids (e.g., methylprednisolone 1 g/day for 3 days).

VI. GVHD

A. General principles: GVHD is a major cause of morbidity and mortality after allogeneic HCT.

B. Etiology/pathophysiology: the GVHD syndrome is caused by donor T cells activated by immunologically disparate HLA and non-HLA antigens in the recipient.

C. Diagnosis.

1. Clinical presentation: acute GVHD (occurring usually before posttransplant day 120) may involve the skin (erythematous rash), GI tract (nausea, vomiting, diarrhea), and rarely liver (hyperbilirubinemia, transaminitis). Chronic GVHD (occurring after posttransplant day 100) has typically a more insidious onset and may involve the skin, eyes, joints, and liver; it is reminiscent of autoimmune diseases such as systemic sclerosis and obstructive lung disease (BO).
2. Laboratory and radiologic studies: skin punch biopsy and GI endoscopy with biopsy confirm the diagnosis in the appropriate clinical setting. Cholestatic jaundice is the hallmark of liver involvement; liver biopsy is rarely required. Pulmonary function test and lung biopsy in patients with presumed BO to rule out infectious etiologies.
3. Differential diagnosis: drug rash, peptic ulceration, and viral or mycotic enteritis should be ruled out. In patients with liver function abnormalities, drug toxicity, sepsis (cholangitis lenta), biliary sludge syndrome, viral infections (CMV, Epstein-Barr virus [EBV], hepatitis B), and concurrent hemolysis should be considered.

D. Treatment. Despite prophylaxis (e.g., cyclosporine plus methotrexate), 40% to 80% of allogeneic HCT recipients develop GVHD. Corticosteroids are standard first-line therapy (e.g., prednisone 1 to 2 mg/kg/d; slow taper after 1 to 2 weeks). Prolonged corticosteroid treatment increases susceptibility to infections. Steroid-refractory patients require second-line immunosuppressive therapy and usually have a poor prognosis.

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Review of thrombotic microangiopathy after allogeneic HCT.

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Comprehensive review of hepatic complications after HCT.

Pene F, Aubron C, Azoulay E, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure support. *J Clin Oncol* 2006;24:643–649.
This retrospective study illustrates that the prognosis of HCT recipients who require mechanical ventilation remains relatively poor in spite of improvements over the past two decades. Patients who require ICU support during the engraftment period have a better prognosis than those who require ICU support due to later HCT complications.

SECTION 15

Rheumatologic and Immunologic Problems in the Intensive Care Unit

Paul F. Dellaripa

139 Rheumatologic Disorders in the Intensive Care Unit

Donough G. Howard

I. OVERVIEW.

This chapter reviews the important rheumatic diseases most likely to be encountered in the intensive care unit (ICU). Brief descriptions and treatment options are discussed with a constant emphasis on the ongoing risk of infectious complications that may lead to critical illness.

II. RHEUMATOID ARTHRITIS

A. General principles. A chronic inflammatory disorder affecting the synovial lining of joints, tendons, and bursae in addition to a large variety of extra-articular structures. The etiology of rheumatoid arthritis (RA) is unknown. Patients may require ICU admission because of disease complications or complications of therapy, typically infections.

B. Treatment. Table 139-1 details current treatment with disease-modifying antirheumatic drugs (DMARDs). As a general rule, immunosuppressive DMARDs should be withheld in critically ill patients.

1. **RA therapy and infection risk.**
   - **a.** Biologic therapy is considered to be associated with an increased risk of infection and with an increase in morbidity and mortality from infection.
   - **b.** The risk of reactivation of latent TB is increased with biologic therapy.
   - **c.** Reactivation of hepatitis B in chronic carriers has also been reported with some biologic therapies.
   - **d.** Rare cases of progressive multifocal leukoencephalopathy (PML) due to reactivation of JC virus has been reported with the use of rituximab.
   - **e.** Biologic and steroid therapy may attenuate the normal presentation of sepsis.

C. System-specific considerations in RA.

1. **Pulmonary.**
   - **a.** Pleural disease.
     - **i.** Pleural inflammation/effusions occur frequently.
     - **ii.** May be asymptomatic or lead to large symptomatic effusions.
     - **iii.** Effusions require aspiration to rule out infection or other causes.
     - **iv.** Effusions are exudative with low glucose levels.
   - **b.** Parenchymal lung involvement.
     - **i.** Interstitial lung disease (ILD).
     - **ii.** Bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia (COP).
     - **iii.** Lung toxicity from medications, principally methotrexate-induced pneumonitis.
     - **iv.** Infection due to immunocompromised state, including tuberculosis.
     - **v.** Pulmonary rheumatoid nodules.
   - **c.** Diagnosis.
     - **i.** Presence of ground glass and reticular changes on high-resolution computed tomography (CT) scanning.
     - **ii.** Bronchoscopy and bronchoalveolar lavage (BAL) are useful to rule out opportunistic infection.
     - **iii.** Open lung biopsy or video-assisted thoracic surgery (VATS) is reserved for cases where there is diagnostic confusion or in patients who have failed to respond to initial treatment.
   - **d.** Treatment.
     - **i.** BOOP and acute methotrexate toxicity tend to be steroid responsive and usually do not require other immunosuppressive agents.
     - **ii.** ILD treatment in RA is controversial. Corticosteroids, mycophenolate, and cyclophosphamide have been used in rapidly advancing disease.

TABLE 139-1 Treatment of RA with DMARDs

	Dose/administration	Class	Adverse reactions	Special considerations
Oral DMARDs				
Methotrexate	7.5–25 mg q wk PO, SC/IM	Dihydrofolate reductase inhibitor	Hepatotoxicity, bone marrow suppression, ILD, decreased resistance to infection	Concomitant use of folic acid recommended, monitor complete blood count (CBC), liver function tests (LFTs)
Leflunomide (Arava)	10–20 mg daily PO	Pyrimidine synthesis inhibitor	Diarrhea, alopecia, rash, hepatotoxicity, decreased resistance to infection, increases hepatotoxicity of other drugs	Metabolized through enterohepatic circulation with half-life of >90° Urgent elimination requires treatment with cholestyramine
TNF inhibitors				
Etanercept (Enbrel)	50 mg q wk SC in single or divided doses	TNF receptor blocker	Sepsis, reactivation of TB	Caution in CHF (NYHA class III/IV); avoid live vaccines; contraindicated in serious infections
Adalimumab (Humira)	40 mg q 2 wk SC	Monoclonal anti-TNF antibody	Sepsis, reactivation of TB	Caution in CHF; avoid live vaccines; contraindicated in serious infections
Certolizumab (Cimzia)	200 mg q 2 wk SC	Pegylated monoclonal anti-TNF antibody	Sepsis, reactivation of TB	Caution in CHF; avoid live vaccines; contraindicated in serious infections

(continued)

TABLE 139-1 Treatment of RA with DMARDs *(continued)*

	Dose/administration	Class	Adverse reactions	Special considerations
Golimumab (Simponi)	50 mg q 4 wk SC	Monoclonal antibody	Sepsis, reactivation of TB	Caution in CHF; avoid live vaccines; contraindicated in serious infections
Infliximab (Remicade)	3–5 mg/kg q 4–8 wk IV infusion	Monoclonal anti-TNF antibody	Sepsis, reactivation of TB, infusion reactions	Caution in CHF; avoid live vaccines; contraindicated in serious infections
Other biologic medications				
Anakinra (Kineret)	100 mg qd SC	IL-1 receptor antagonist	Diarrhea, increased risk of infection	Avoid live vaccines; not used in combination with other biologic DMARDs
Rituximab (Rituxan)	1,000 mg IV on day 1 and 15 repeated q 6 mo	Monoclonal anti-CD20 antibody	Sepsis, infusion reactions	Patients remain B-cell depleted and immunocompromised for months after treatment; rare cases of PML due to reactivation of JC virus have been reported; not used in combination with other biologic DMARDs

Abatacept (Orencia)	500–1,000 mg IV q 4 wk	Inhibits T-cell activation	Sepsis, may exacerbate COPD	Reactivation of TB, reactivation of hepatitis B reported; avoid live vaccines; not used in combination with other biologic DMARDs
Tocilizumab	8 mg/kg IV q 4 wk	IL-6 inhibition	Sepsis, infusion reactions, increased liver transaminases, hypercholesterolemia	Reactivation of TB, monitor aspartate aminotransferase or alanine aminotransferase (AST/ALT) every 4–8 wk for first 6 mo, avoid live vaccines; not used in combination with other biologic DMARDs
Tofacitinib	5 mg b.i.d PO	Janus kinase inhibitor	Infections including opportunistic. hyperlipidemia, cytopenias	New class of DMARD recently licensed

PO, per oral; mg, milligram; SC, subcutaneous; IM, intramuscular; TNF, tumor necrosis factor; TB, tuberculosis; CHF, congestive heart failure; IV, intravenous; COPD, chronic obstructive pulmonary disease; DMARDs, disease-modifying antirheumatic drugs; IL-1, interleukin 1.

2. **Neurologic involvement.**
   a. Spinal cord compression due to cervical vertebral instability is one of the most common neurologic sequelae of long-standing severe RA.
   b. Synovitis damages the transverse ligament leading to subluxation of the odontoid peg of C2, compressing the spinal cord and brainstem. This area is particularly vulnerable during endotracheal intubation or endoscopy.
   c. Patients with long-standing RA should ideally be screened with flexion and extension imaging of the cervical spine before any intubation.
   d. If instability is present or even suspected, endoscopic intubation following neck stabilization should be undertaken.

III. CRYSTAL ARTHROPATHY

A. Gout. Acute attacks represent an inflammatory reaction to the crystalline form of uric acid when it precipitates in joints and/or soft tissues. Attacks may involve one or more joints, typically the first metatarsophalangeal (MTP) joint, ankle, knee, or wrist.

1. **Pathogenesis.**
   a. Sudden fluxes in serum uric acid levels facilitate uric acid crystallization in joints.
   b. Uric acid levels are sensitive to the use of intravenous (IV) fluids, dietary changes, and the use of a variety of medications.
2. **General principles.**
   a. Acute attacks lead to the sudden onset of severe pain and tenderness, with erythema and warmth over the affected joint, which can include nearly any joint.
   b. Low-grade fever is common, especially if more than one joint is involved.
3. **Diagnosis.**
   a. Diagnosed by demonstrating the presence of intracellular monosodium urate crystals on polarized microscopy of synovial fluid.
   b. Synovial fluid white blood cell (WBC) counts may vary from 5,000 to 80,000/mm^3.
4. **Treatment** (Table 139-2).

B. Pseudogout.

1. **General.**
   a. Caused by the presence of intra-articular calcium pyrophosphate crystals.
   b. Typically affects knees or hands.
   c. Clinical appearance identical to that of gout.
2. **Diagnosis.** Synovial fluid aspiration shows the presence of intracellular weakly positively birefringent rhomboid crystals. Plain radiographs may show chondrocalcinosis indicating chronic calcium pyrophosphate within the joint.
3. **Treatment.**
   a. Identical to that for gout.

TABLE 139-2 Treatment of Gout in the ICU

Drug	Dosage	Adverse reaction	Special considerations
Colchicine	0.6 mg PO up to three doses	GI toxicity (nausea, diarrhea), bone marrow suppression (granulocytopenia)	Dosage needs to be adjusted for renal function; IV dosing is highly discouraged
Corticosteroids—prednisone	20–40 mg qd PO for 2–3 d, then taper over 1 wk	Immune suppression hyperglycemia	PO route is usually not appropriate in patients in ICU
Anakinra	100 mg SC daily	Injection site reactions	
Intra-articular steroid	Doses varied depending on joint involved	If high suspicion of joint infection, wait for Gram stain result	
IV steroids	Methylprednisolone 15–80 mg Triamcinolone 10–40 mg		

PO, per oral; mg, milligram; GI, gastrointestinal; IV, intravenous; ICU, intensive care unit.

b. Joint aspiration may be sufficient to resolve some cases.
c. Colchicine is less effective compared to gout.

C. Other crystal arthritides. Rarer forms of crystal arthropathy include those caused by calcium oxalate and calcium hydroxyapatite, which tend to occur in individuals on dialysis.

IV. SEPTIC ARTHRITIS

A. General principles.

1. Bones, joints, and bursae may be infected with a large variety of microorganisms.
2. *Staphylococcus aureus* is the most common cause of musculoskeletal infection.
3. Other microorganisms are increasing in prevalence.
4. Most cases are acute with swelling, pain, surrounding erythema, and loss of joint function.
5. Monoarticular involvement is most common, but several joints may be affected with hematogenous spread.
6. Fever is usually present but is not invariable.

B. Diagnosis.

1. Immediate joint aspiration is imperative in any suspected case.
2. Synovial fluid should be sent for the following.
   a. Gram stain.
   b. Cell count and differential cell count.
   c. Culture and sensitivity.
   d. Polarized microscopy for crystals.
3. Cell count may vary but is usually >50,000/mm^3.
4. The presence of crystals does not out rule the possibility of infection.

C. Treatment.

1. Repeated daily aspirations or surgical washout is essential.
2. Empiric antibiotic therapy should be initiated following a stat Gram stain and antibiotics adjusted once cultures become available (Table 139-3).

TABLE 139-3 Antibiotics in Septic Arthritis

Clinical setting	Top three microorganisms	Initial empiric antibiotic choice
Nonimmunocompromised, not sexually active	1. *Staphylococcus aureus* 2. *Streptococcus* 3. Gram-negative bacilli	Vancomycin or third-generation cephalosporin depending on results of Gram stain
Nonimmunocompromised, sexually active	1. *Neisseria gonorrhoeae* 2. *Staphylococcus aureus* 3. Streptococci	Gram stain negative—third-generation cephalosporin Gram stain shows gram-positive cocci in clusters—vancomycin pending sensitivity If *N. gonorrhoeae* suspected (Gram-negative diplococci), then ceftriaxone and azithromycin
Prosthetic joints	1. *Staphylococcus epidermidis* 2. *Staphylococcus aureus* 3. Enterobacteriaceae	Vancomycin and third-generation cephalosporin or ciprofloxacin until Gram stain and cultures available; consider addition of aminoglycoside if *Pseudomonas* suspected
Immunocompromised	*Large variety of organisms possible*	Vancomycin and third-generation cephalosporin until cultures available; seek I. D. input early

3. The joint should be rested with physical therapy referral to prevent contractures.
4. Baseline radiographs should be obtained to follow progress.
5. Baseline C-reactive protein (CRP) may be helpful in monitoring longer term therapeutic response.
6. Fungal joint infection is rare, more indolent in presentation, and occurs usually in immunocompromised patients.
7. Fungal components are normally visible on Gram stain, allowing for early initiation of antifungal therapy.

V. ANTIPHOSPHOLIPID ANTIBODY SYNDROME.

Defined as recurrent arterial or venous thrombosis often associated with fetal losses in the presence of anticardiolipin antibodies or lupus anticoagulant. It may be primary or may be associated with another connective tissue disease.

A. Diagnosis.

Clinical features include the following.

1. One or more episodes of arterial or venous thrombosis or both.
2. Fetal death or recurrent spontaneous abortion.
3. Other features include thrombocytopenia, livedo reticularis, cardiac valvular lesions, migraine headaches, chorea, and leg ulcers.
4. Presence of either anticardiolipin antibody immunoglobulin M (IgM) or IgG in medium or high titer or lupus anticoagulant on two occasions, at least 6 weeks apart.

B. Treatment.

1. Anticoagulation with heparin followed by lifelong warfarin is indicated. See recently published guidelines on managing long-term anticoagulation (Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008;133(6):160S–198S).
2. The catastrophic antiphospholipid antibody defines a syndrome involving widespread thrombosis with life-threatening illness. Treatment may include corticosteroids, cyclophosphamide, plasmapheresis, anticoagulation, and possibly rituximab.

VI. IDIOPATHIC INFLAMMATORY MYOSITIS.

Polymyositis and dermatomyositis are inflammatory muscle diseases characterized by proximal muscle weakness, elevated muscle enzymes, and characteristic cutaneous features.

A. Diagnosis.

Clinical features include the following.

1. Proximal girdle and shoulder weakness.
2. Skin involvement includes Gottron papules (an erythematous and often scaly eruption typically seen symmetrically over the extensor surfaces of the metacarpophalangeal [MCP] and to a lesser extent the interphalangeal joints and elbows); erythema of the neck, chest, and forehead; heliotrope rash; and periungual erythema.
3. Dysphagia and aspiration pneumonia.
4. ILD, especially in patients who are Jo-1 antibody positive.
5. Cardiomyopathy, arrhythmias, and congestive heart failure.

B. Treatment.

1. High-dose corticosteroids with consideration for an additional agent such as methotrexate.
2. In progressive ILD, high-dose steroids with cyclophosphamide are indicated. Other agents such as mycophenolate, tacrolimus, and azathioprine may be used.

VII. SYSTEMIC LUPUS ERYTHEMATOSUS

A. General principles. An inflammatory disorder of unknown etiology characterized by antibody production, immune complex deposition, and a wide variety of organ and system involvement. Diagnosis is based on the presence of characteristic clinical features and laboratory findings, including decreased complement levels, cytopenias, and typical autoantibody profiles.

B. Renal involvement. Occurs in 50% of patients. Treatment protocols exist, depending on the histologic classification on renal biopsy, with active nephritis requiring treatment with high-dose corticosteroids and cyclophosphamide or mycophenolate.

C. Pulmonary involvement.

1. Pleuritis is the most common pulmonary manifestation of systemic lupus erythematosus (SLE), affecting approximately 50% of SLE patients.
2. Pulmonary hemorrhage is a rare but serious complication of SLE.
   a. Patients, frequently young females, present with severe hypoxia, patchy infiltrates, and hemoptysis.
   b. Treatment is with high-dose corticosteroids and immunosuppressive agents with a potential role for plasmapheresis.
   c. Pulmonary hypertension is a rare but well recognized complication of SLE.

D. Hematologic.

1. Autoimmune hemolytic anemias respond well to high-dose steroids; other immunosuppressants, rituximab, and splenectomy are options for unresponsive cases.
2. Idiopathic thrombocytopenic purpura (ITP) can also occur; treatment is with high-dose oral or IV steroids and if needed IV immunoglobulin.

E. Neurologic.

1. Neuropsychiatric lupus is the name given to the large variety of neurologic presentations seen in SLE.
2. These include seizure disorders, stroke disease, demyelinating disorders, psychosis, transverse myelopathy, peripheral neuropathy, and headache.

VIII. SCLERODERMA

A. General principles. Multisystem disease characterized by tissue inflammation and fibrosis with vascular involvement leading to episodic vasospasm and tissue ischemia.

B. Interstitial lung disease. Frequent complication and the leading cause of death.

1. High-resolution CT findings range from ground glass opacities to honeycombing.
2. BAL shows an elevated neutrophil and eosinophil count; pulmonary function tests show a restrictive pattern.
3. Treatment including cyclophosphamide combined with corticosteroids although newer therapies are emerging.

C. Pulmonary hypertension.

1. Complication of typically long-standing limited scleroderma.
2. Diagnosis is suggested by echocardiography or an otherwise unexplained elevation of the B-type natriuretic peptide (BNP) and confirmed on right heart catheterization.
3. Treatment with IV and inhaled prostacyclins, phosphodiesterase inhibitors, and endothelin antagonists.

D. Scleroderma renal crisis.

1. Renal crisis is a syndrome of rapidly progressive hypertensive renal failure.
2. Accompanied by microvascular hemolysis.
3. The associated hyperreninemic state drives the process, and treatment is therefore with urgent administration of high-dose angiotensin-converting enzyme inhibitors.
4. Rarely, normotensive renal crisis can occur.
5. Occurs more commonly in those who are RNA polymerase III antibody positive.

E. Gastrointestinal.

1. Constipation due to decreased peristalsis with pseudo-obstruction a possibility.
2. Diarrhea due to bacterial overgrowth.
3. Gastroesophageal reflux disease (GERD) is almost universal.
4. Enteral nutrition should be maintained when possible in the ICU setting.

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140 Anaphylaxis

Helen M. Hollingsworth
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I. GENERAL PRINCIPLES

A. Anaphylaxis is a severe and potentially fatal form of immediate hypersensitivity (immunoglobulin E [IgE]-mediated antigen recognition). An *anaphylactoid reaction* is caused by a mechanism other than IgE recognition of antigen.

B. In this chapter, IgE-mediated and non–IgE-mediated reactions are referred to as *anaphylactic reactions*.

II. PATHOPHYSIOLOGY

A. Binding of allergenic antigen (Table 140-1) to adjacent IgE molecules on sensitized mast cells/basophils activates synthesis and secretion of mediators of anaphylaxis, such as histamine, leukotrienes (LTC4, LTD4, and LTE4), and cytokines.

B. Mast cell and basophil activation also occur through a variety of non–IgE-mediated mechanisms (Table 140-2).

III. CLINICAL FEATURES

A. The major clinical features of anaphylaxis are urticaria, angioedema, respiratory obstruction (stridor, wheezing, breathlessness), and vascular collapse (dizziness, hypotension, loss of consciousness), with urticaria being the most common.

B. Additional clinical manifestations include a sense of impending doom, rhinorrhea, generalized pruritus and swelling, dysphagia, vomiting, and abdominal pain.

C. **Physical examination** of a patient with anaphylactic shock often reveals a rapid, weak, irregular, or unobtainable pulse; tachypnea, respiratory distress, cyanosis, hoarseness, or stridor, diminished breath sounds, wheezing, and hyperinflated lungs; urticaria, angioedema, or conjunctival edema. Only a subset of these may occur in any given patient.

D. **Laboratory findings** include elevation of blood histamine and mature β-tryptase, and total tryptase levels, low complement levels, and disseminated intravascular coagulation (DIC). Documentation of an elevated serum or plasma total tryptase at the time of the reaction compared with baseline levels provides support for diagnosis of anaphylaxis. A normal tryptase level does not exclude anaphylaxis.

E. Arrhythmias may occur.

TABLE 140-1 Causes of IgE-mediated Anaphylaxis

Type	Agent	Example
Proteins	Allergen extracts	Pollen, dust mite, mold, animal dander
	Enzymes	Chymopapain, streptokinase, L-asparaginase
	Food	Egg white, legumes, milk, nuts, shellfish, wheat
	Heterologous serum	Tetanus antitoxin, antithymocyte globulin, snake antivenom
	Hormones	Insulin, ACTH, TSH, progesterone, salmon calcitonin
	Vaccines	Influenza
	Venoms	Hymenoptera
	Others	Heparin, latex, thiobarbiturates, seminal fluid
Haptens	Antibiotics	β-Lactams, ethambutol, sulfonamides, vancomycin
	Disinfectants	Ethylene oxide
	Local anesthetics[a]	Benzocaine, tetracaine, xylocaine, mepivacaine
	Others	Cisplatin, carboplatin

[a]Precise mechanism not established.
ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

TABLE 140-2 Causes of Non–IgE-mediated Anaphylaxis

Complement activation
Blood product transfusion in an IgA-deficient patient
Hemodialysis[a]
Direct release of chemical mediators of anaphylaxis
Protamine[a]
RCM
Ketamine
ACE inhibitors[a]
Local anesthetics[a]
Codeine and other opiate narcotics
Highly charged antibiotics, including amphotericin B
Nonsteroidal anti-inflammatory medications (NSAIDs)[b]
Antineoplastic agents (e.g., paclitaxel[a], etoposide[a])
Sulfiting agents
Exercise[c]
Idiopathic recurrent anaphylaxis

[a]Precise mechanism not established. May be due to combination of factors.
[b]Some NSAIDs cause anaphylaxis through an IgE-dependent mechanism.
[c]A costimulus such as a food, medication, or cold exposure is usually involved.

IV. DIAGNOSIS

A. The rapid onset and progression of typical symptoms to a severe and sometimes fatal outcome after exposure to a typical antigen or inciting agent are characteristic of anaphylaxis.

B. Mild systemic reactions often last for several hours, but rarely >24 hours.

C. Severe manifestations (e.g., laryngeal edema, bronchoconstriction, hypotension), if not fatal, can persist or recur for several days, but sometimes resolve within minutes of treatment.

V. TREATMENT: GENERAL CARDIOPULMONARY SUPPORTIVE MEASURES

A. Oxygen saturation, blood pressure, cardiac rate, and rhythm should be monitored closely, and supplemental oxygen administered.

B. Intubation and assisted ventilation may be necessary for laryngeal edema or severe bronchoconstriction.

C. Occasionally, cricothyroidotomy is necessary.

D. One characteristic of patients with biphasic or protracted anaphylaxis is oral ingestion of the offending antigen. Oral administration of activated charcoal and sorbitol may reduce absorption and duration of exposure to the antigen.

VI. TREATMENT: PHARMACOLOGIC

(Table 140-3).

A. Adrenergic agents.

1. Epinephrine should be given promptly to treat all initial manifestations of anaphylaxis; a delay in administration of epinephrine may be fatal.
2. In adults, the dose of epinephrine hydrochloride (1 mg/mL) is 0.3 to 0.5 mL intramuscularly (IM) in the mid-anterolateral thigh. This may be repeated in 5 to 15 minutes. In children, the dose is 0.01 mg/kg (maximum per dose 0.5 mg) IM in the mid-anterolateral thigh and may be repeated in 5 to 15 minutes.

B. Antihistamines.

1. H_1 receptor–blocking antihistamines reverse histamine-induced vasodilatation, tachycardia, and bronchoconstriction, as well as cutaneous manifestations, but are insufficient to treat anaphylaxis in the absence of epinephrine.
2. H_2 receptor–blocking antihistamines are often prescribed, although evidence of benefit is limited.

C. Glucocorticoids.

1. Systemic glucocorticoids increase tissue responses to β-adrenergic agonists and inhibit generation of LTC4, LTD4, and LTE4.
2. Glucocorticoids may prevent late recurrences of anaphylaxis, although biphasic anaphylaxis occurs in 20% of anaphylactic reactions despite glucocorticoid therapy.

TABLE 140-3 Treatment of Anaphylaxis in Adults

Mandatory and immediate

General measures
- Administer aqueous epinephrine (1 mg/mL), 0.3–0.5 mL IM in the mid-anterolateral thigh, up to 3 doses at 1- to 5-min intervals
- Apply a tourniquet proximal to the antigen injection or sting site
- Administer supplemental oxygen

For laryngeal obstruction or respiratory arrest
- Establish airway using endotracheal intubation, cricothyroidotomy, or tracheotomy
- Initiate mechanical ventilation

After clinical appraisal

General measures
- Diphenhydramine, 1.25 mg/kg to maximum of 50 mg, IV or IM
- Aqueous hydrocortisone, 200 mg; dexamethasone, 10 mg; or methylprednisolone, 125 mg; IV every 6 h for 24–48 h
- Cimetidine, 300 mg, or ranitidine 50 mg, IV over 3–5 min

For hypotension
- Aqueous epinephrine (1 mg/mL), 1 mL in 500 mL of saline at 1–5.0 mL/min, or 2 to 10 μg/min titrated to maintain a mean arterial pressure (MAP) of 65 mm Hg, by an infusion pump through a central venous line.
- Volume expansion with normal saline.
- Norepinephrine 4 mg in 1,000 mL of D5W at 2–12 μg/min IV.
- Glucagon (if patient is receiving β-blocker therapy) 1 to 5 mg IV bolus or infusion or 1 mg/L of D5W at a rate of 5–15 mL/min.

For bronchoconstriction
- Supplemental oxygen
- Albuterol (0.5%), 0.5 mL in 2.5 mL of saline, by a nebulizer. If intubated, use albuterol-metered dose inhaler (MDI) 10–20 puffs, endotracheally, every 20 min, as needed.

VII. PREVENTION OF ANAPHYLACTIC REACTIONS

A. A careful history identifying possible precipitants of anaphylaxis at the time of presentation is crucial.

B. Patients should be encouraged to wear a MedicAlert (MedicAlert Foundation, 2323 Colorado Ave., Turlock, CA 95382 or www.medicalert.org) or a similar identifying bracelet.

C. Patients should carry two epinephrine devices (e.g., EpiPen or EpiPen, Jr.) for intramuscular injection.

D. β-Blocking medication may increase the risk of anaphylaxis and make it more refractory to treatment; therefore, β-blocking medication should be avoided, if possible, in patients at risk for recurrent anaphylaxis.

VIII. MANAGEMENT OF ANAPHYLAXIS TO SPECIFIC PRECIPITANTS

A. For patients with a history of anaphylaxis to penicillin and related antibiotics who are admitted to the intensive care unit (ICU) and need antibiotic therapy:

1. Approximately 10% of allergic reactions to β-lactams are life threatening: of these, 2% to 10% are fatal.
2. Skin testing that includes both major (PrePen) and minor (Penicillin G 10,000 units/mL) determinants can detect IgE-mediated sensitivity, but it does not evaluate other types of sensitivity, such as serum sickness reactions, morbilliform rashes, and interstitial nephritis.
3. IgE-mediated cross-reactivity between penicillins carbapenems is high, so desensitization is needed if administration of a carbapenem is necessary.
4. If skin testing for the major and minor penicillin determinants is negative, cephalosporins may be administered. The risk of a reaction is <1%. If penicillin skin testing is positive, a graded challenge or desensitization to the indicated cephalosporin is necessary. If penicillin skin testing is not available, then desensitization to the indicated cephalosporin is performed.
5. Patients allergic to amoxicillin/ampicillin (but not penicillin) may have cross reactivity with certain cephalosporins, although not usually with ceftriaxone or ceftazidime.
6. Monobactams (e.g., aztreonam) do not show cross-reactivity with penicillins, but may cross-react with the cephalosporins.
7. For less severe reactions and when no alternative agent is available, desensitization may be attempted in the ICU setting. Five to six 10-fold dilutions of the target concentration are administered in sequence, starting with the most dilute and progressing to the next stronger concentration every 15 to 20 minutes, as tolerated.

B. Stinging insect venom anaphylaxis:

1. After initial treatment, patients should be referred to an allergist for skin testing and possible desensitization.
2. Specific venom desensitization provides >95% protection against anaphylaxis on subsequent stings.

C. Food anaphylaxis.

1. Eggs, milk, peanuts, soy, tree nuts, wheat, fish, and shellfish are the most commonly implicated foods. Sensitivity is confirmed by serum immunoassay.
2. Strict avoidance of implicated foods and careful education about prompt administration of epinephrine at the onset of a reaction are essential.

D. Radiographic contrast medium anaphylaxis.

1. Radiographic contrast media (RCM) are classified based on osmolality, ionicity, and whether they are monomers or dimers. In patients with a history of a previous radiocontrast medium anaphylactic reaction, the repeat reaction rate is reported to be 35% to 60%.
2. Patients with a general history of allergies (e.g., inhalant allergens, foods, medications) have an increased RCM reaction rate. However,

pretreatment of such patients is not suggested for studies using a nonionic low osmolal agent, as long as the patient has not had a prior reaction to RCM. Asthma should be well controlled prior to the procedure.

3. For patients with a history of RCM anaphylaxis, use of low ionic contrast or alternative imaging studies (e.g., computed tomography with a gadolinium-based agent, magnetic resonance imaging, or ultrasound) should be considered.
4. Pretreatment with glucocorticoids (50 mg prednisone, 13 hours, 7 hours, and 1 hour before administration) and diphenhydramine (50 mg orally or IM 1 hour before administration) with or without ephedrine (25 mg orally 1 hour before administration) may reduce the reaction rate to RCM.
5. For an emergent procedure, hydrocortisone (200 mg) can be given intravenously (IV) immediately and repeated every 4 hours until the procedure in addition to diphenhydramine (50 mg IV) immediately before the procedure.

E. Latex-induced anaphylaxis.

1. Latex is found in a broad spectrum of medical products. Health care workers and patients with spina bifida or a history of multiple medical procedures are at increased risk of latex-induced anaphylaxis.
2. Serum immunoassay (CAP-Pharmacia) to latex is helpful, but may have false-negative results (50% to 60% sensitivity).
3. Standardized skin testing is not commercially available.
4. Patients with latex allergy should be cared for in latex-free operating rooms, ICUs, and hospital rooms.

F. Angiotensin-converting enzyme (ACE) inhibitor anaphylaxis.

1. Severe, potentially life-threatening facial and oropharyngeal angioedema can occur in individuals with sensitivity to ACE inhibitors and angiotensin receptor blockers (ARBs).
2. Onset of angioedema usually starts within the first several hours or up to a week after beginning therapy, but may be delayed for months to years.
3. Cross-reactivity does occur among the different ACE inhibitors, but usually not between ACE inhibitors and ARBs.
4. Epinephrine is not always helpful: endotracheal intubation or cricothyroidotomy may be necessary to maintain an airway. Angioedema may take 1 to 3 days to resolve. Antihistamines and systemic glucocorticoids are frequently administered, although evidence of benefit is limited.
5. The bradykinin antagonist icatibant or fresh frozen plasma (FFP) may be effective for severe or persistent cases.

G. Hereditary angioedema (HAE).

1. Individuals with absent or inactive C1 esterase inhibitor can develop life-threatening angioedema of the upper respiratory tract.
2. Urticaria is generally not present, but a history of recurrent abdominal pain from intestinal angioedema may be elicited.
3. Acutely, complement C2 and C4 levels are low; C1q is normal in the hereditary form and low in the acquired form.
4. C1 esterase inhibitor is either low or nonfunctional.
5. Angioedema is frequently refractory to epinephrine, necessitating intubation or cricothyroidotomy. Antihistamines and glucocorticoids are NOT effective.

6. C1-inhibitor replacement protein (concentrate) can be administered IV for acute attacks. The dosing is 20 units/kg, infused over 10 minutes.
7. Ecallantide, the recombinant kallikrein inhibitor, is given for acute attacks of HAE. The adult dose is 30 mg administered in three separate 10-mg subcutaneous injections to the abdominal wall. It may cause allergic reactions and anaphylaxis.
8. Icatibant is a synthetic polypeptide that competitively antagonizes bradykinin. The dose in adults is 30 mg administered by subcutaneous injection/infusion in a location 5 to 10 cm below the umbilicus over a minimum of 30 seconds.
9. FFP is considered a second-line therapy to be used when the C1-inhibitor concentrate, icatibant, and ecallantide are not available. FFP may be given in 2 units every 2 to 4 hours until symptoms improve.

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141 Vasculitis in the Intensive Care Unit

Paul F. Dellaripa

I. OVERVIEW.

A group of disorders in which inflammation and necrosis of blood vessels lead to organ dysfunction due to the development of thrombosis or hemorrhage. Mimics of vasculitis include subacute bacterial endocarditis, atrial myxoma, antiphospholipid syndrome, and cholesterol embolism.

II. GRANULOMATOSIS WITH POLYANGIITIS (GPA) (formerly referred to as Wegener granulomatosis)

A. General principles.

1. Characterized by granulomatous inflammation of the upper and lower respiratory tract, segmental necrotizing glomerulonephritis, and small vessel inflammation of other organ systems.
2. Reasons for intensive care unit (ICU) admission for GPA and all of the vasculitides include respiratory failure due to alveolar hemorrhage, rapidly progressive renal failure, and infections, including those due to immunosuppressive treatment of disease. Stridor due to subglottic stenosis can occur in GPA.

B. Pathogenesis.

1. There is no known etiologic agent for GPA.
2. Antineutrophilic cytoplasmic antibodies (ANCA) are present in >90% of cases of GPA. C-ANCA (with specificity to PR3 antigen) seen in 90% and P-ANCA (with specificity to myeloperoxidase [MPO]) seen in a minority of cases.

C. Diagnosis.

1. Clinical presentation typically includes sinusitis, rhinitis, epistaxis, otitis media, and hearing loss.
2. Lower respiratory tract is involved frequently, with cough, dyspnea, hemoptysis, and progressive respiratory failure due to alveolar hemorrhage. Pulmonary infiltrates may be diffuse, patchy, nodular, or cavitary. Lung biopsy may be necessary to confirm diagnosis and eliminate the possibility of mycobacterial or fungal disease.
3. Renal involvement may be rapidly progressive leading to dialysis. Rarely, ANCA-associated vasculitis coexists with antiglomerular basement antibodies (anti–glomerular basement membrane [GBM]). Diagnosis is confirmed based on clinical findings, presence of ANCA, and tissue biopsy

of affected organs, including the kidney, lung, eye, nerve, or skin. In some cases, tissue biopsy may not be necessary when the clinical suspicion for disease is high, and the ANCA pattern unequivocally supports the diagnosis.

D. Treatment.

1. In the setting of severe disease (respiratory failure, alveolar hemorrhage, and progressive renal failure), therapy should include cyclophosphamide (CYC) or rituximab (375 mg/m^2 weekly for 4 weeks or 1 g twice separated by 2 weeks) and high-dose corticosteroids. Intravenous (IV) methylprednisolone in doses of 1,000 mg/day for 3 days may be considered.
2. Oral dosing of CYC is 2 mg/kg but, in renal failure, it is as follows: 1.5 mg/kg/d if creatinine clearance (CrCl) is 50 to 99; 1.2 mg/kg/d if CrCl is 25 to 49; 1.0 mg/kg/d if CrCl is 15 to 24; and 0.8 mg/kg/d if CrCl is <15 or dialysis.
3. In the setting of critical illness and potential variability of gastrointestinal (GI) absorption, IV CYC (0.5 g/m^2 to 1 g/m^2) may be indicated. Appropriate IV hydration pre- and post-CYC infusion and addition of MESNA are important.
4. *Pneumocystis* pneumonia (PCP) prophylaxis should be offered.
5. Plasmapheresis and IV immunoglobulin (Ig) may be useful during pregnancy or in severe or refractory GPA and severe alveolar hemorrhage with or without anti-GBM antibodies.
6. The presence of worsening pulmonary infiltrates in those treated with CYC and steroids raises the suspicion of fungal infections and PCP, warranting early bronchoscopy or biopsy and early consideration for antifungal and PCP therapy.
7. Other agents such as mycophenolate mofetil, azathioprine, or methotrexate may be used in less severe cases or in refractory cases.

III. MICROSCOPIC POLYANGIITIS

A. General principles.

1. Small- and medium-vessel necrotizing vasculitis presenting with pauci-immune segmental necrotizing glomerulonephritis and pulmonary capillaritis with alveolar hemorrhage.
2. ANCA (P-ANCA with MPO specificity) is positive in 70% of cases.
3. Clinical presentation can overlap with GPA, though pathologically there is lack of granulomas.

B. Diagnosis. Biopsy of appropriate tissue, typically the kidney, lung, or nerve, in conjunction with ANCA positivity.

C. Treatment. Treatment similar to that for GPA.

IV. EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA) PREVIOUSLY KNOWN AS CHURG-STRAUSS SYNDROME (CSS)

A. General principles.

1. Characterized by eosinophilic infiltrates and granulomas in the respiratory tract in the setting of a history of asthma and eosinophilia.

2. Peripheral neuropathy, mesenteric ischemia, cardiac, and central nervous system (CNS) involvement may occur. Renal involvement and alveolar hemorrhage are rare.

B. Diagnosis. ANCA is positive in 60% of patients, mostly MPO pattern. Biopsy of suspected organs shows granulomas and fibrinoid necrosis.

C. Treatment.

1. Corticosteroids in milder presentation, with CYC or rituximab or other immunosuppressant agent in more severe disease.
2. Five-factor score (proteinuria >1 g/day, azotemia, GI or CNS dysfunction, cardiomyopathy) may help to determine prognosis and level of treatment.

V. POLYARTERITIS NODOSA (PAN)

A. General principles. Systemic necrotizing vasculitis involving small and medium muscular arteries.

B. Etiology. The etiology of PAN is unknown, though, rarely, the presence of circulating hepatitis B surface antigen in vessel walls is noted.

C. Diagnosis.

1. Presents with a prodrome of malaise, fatigue, fever, and weight loss.
2. Vasculitic lesions may result in mononeuritis multiplex, cutaneous lesions, intestinal ischemia, myocardial infarction, and congestive heart failure.
3. Laboratory findings include anemia and elevated sedimentation rate. ANCA is absent.
4. Diagnosis is confirmed by tissue biopsy or evidence of microaneurysms on mesenteric angiogram.

D. Treatment.

1. High-dose corticosteroid therapy orally or intravenously with pulse methylprednisolone at 1 g/day for 3 days; CYC used in severe cases.
2. In cases associated with hepatitis B, antiviral therapy may be used in early conjunction with corticosteroids and plasmapheresis.

VI. CRYOGLOBULINEMIC VASCULITIS

A. General principles. Cryoglobulins are Igs that precipitate in the cold. There are three types, with types II and III closely, though not exclusively, associated with hepatitis C infection.

B. Diagnosis.

1. Findings include palpable purpura, peripheral neuropathy, and infrequently life-threatening renal, GI, and pulmonary involvement, including pulmonary hemorrhage.
2. Laboratory values include low complement levels (C4), abnormal liver enzymes, and positive rheumatoid factor.

C. Treatment.

1. Treatment consists of high-dose corticosteroid and adding rituximab or CYC in cases of renal failure or mononeuritis multiplex, as well as treatment for hepatitis C when present.
2. Plasmapheresis or cryofiltration may be beneficial in severe cases.

VII. PULMONARY CAPILLARITIS

A. General principles.

1. Pathologically, pulmonary capillaritis is due to alveolar wall inflammation that leads to disruption of the integrity of the alveolar capillary basement membrane, presenting clinically as diffuse alveolar hemorrhage (DAH).
   a. It is most often associated with immune-mediated processes such as GPA, microscopic polyangiitis, the antiphospholipid antibody syndrome, systemic lupus erythematosus (SLE), Henoch Schönlein purpura, IgA nephropathy, and drug-induced vasculitis such as propylthiouracil.
2. Clinically, pulmonary capillaritis may be an isolated phenomenon or can be seen in concert with other systemic manifestations, including glomerulonephritis, known as the so-called pulmonary renal syndrome.

B. Diagnosis.

1. In patients with evidence of either isolated alveolar hemorrhage or pulmonary renal syndrome, assessment of ANCA, antinuclear antibody (ANA), anti-GBM, and antiphospholipid antibodies is appropriate.
2. Biopsy of the lung or kidney may be useful, though may be difficult to accomplish in the setting of critical illness.

C. Treatment.

1. Treatment consists of empiric high-dose steroids 1 g/day IV for 3 days, cytotoxic therapy, and consideration for plasmapheresis if respiratory or renal failure is severe. In established cases of vasculitis in patients already on immunosuppression, DAH should also raise suspicion for infections such as *Aspergillus*.

VIII. VASCULITIS OF THE CENTRAL NERVOUS SYSTEM

A. General principles. Heterogeneous group of neurologic disorders divided into primary angiitis of the CNS (PACNS) and secondary forms related to rheumatic syndromes such as SLE, rheumatoid arthritis (RA), sarcoidosis, Sjögren, and Behcet syndromes as well as various infections. A condition known as reversible cerebral vasoconstriction syndrome can present with features similar to PACNS, though symptoms are more abrupt in onset, of shorter duration, and with angiographic findings that resolve over a period of weeks. The focus of this section is on PACNS.

B. Diagnosis.

1. PACNS: usually a slow, progressive process characterized by headache, focal deficits, and changes in higher cortical function.
   a. Lumbar puncture reveals mononuclear pleocytosis and elevated protein.
   b. **Magnetic resonance imaging** (MRI) shows abnormal multifocal vascular lesions and leptomeningeal enhancement.
   c. Angiography is nonspecific or normal in up to 60% of cases.
   d. Biopsy of the cortex and leptominges showing granulomas and giant cells is the diagnostic procedure of choice.

C. Treatment. PACNS is treated with corticosteroids and CYC.

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SECTION 16

Psychiatric Issues in Intensive Care

John Querques

142 Diagnosis and Treatment of Agitation and Delirium in the Intensive Care Unit Patient

Jason P. Caplan

I. GENERAL PRINCIPLES

A. Definition.

1. Agitation is a frequent behavioral aberration in severely ill patients, which carries significant risks for the safety of the patient and staff.
2. Agitation may be a symptom of delirium (a neuropsychiatric manifestation of a systemic disturbance), the most common cause of agitation in the intensive care unit (ICU). Delirium is defined as alterations in attention and cognition that develop over hours to days and wax and wane. The hallmark of delirium is inattention that can be gauged by simple bedside testing (e.g., attention to conversation, serial subtraction of 7 from 100, recitation of the months of the year backwards).

B. Epidemiology.

1. Delirium occurs in >30% of all patients in the ICU and in >80% of patients in the ICU who are intubated.

C. Risk factors.

1. Acute physiologic risk factors include metabolic disturbances, infection, shock, hypoxia, renal failure, hepatic failure, and intracranial processes.

2. Chronic physiologic risk factors include advanced age; malnutrition; alcohol or drug abuse; and prior diagnoses of depression, dementia, stroke, seizure, congestive heart failure, or human immunodeficiency virus infection.

3. Iatrogenic risk factors include medication side effects (most commonly those of anticholinergics, benzodiazepines, opioids, antihistamines, and steroids) and the presence of indwelling catheters.

II. ETIOLOGY AND PATHOGENESIS

A. The mnemonic "WWHHHHIMPS" aids recall of the life-threatening causes of delirium (Table 142-1).

B. The current leading hypothesis on the neural mechanism of delirium implicates hypocholinergic and hyperdopaminergic states.

C. Acetylcholine is the primary neurotransmitter of the reticular activating system, a network vital to both alertness and attention. Therefore, a relative cholinergic deficit is likely to disrupt these functions.

D. Impaired oxidative metabolism increases the release, and disrupts the reuptake and extracellular metabolism, of dopamine. Excess dopamine is associated with hallucinations, delusions, and other psychotic symptoms, and may facilitate the excitatory effects of glutamate, thereby producing agitation.

TABLE 142-1 WWHHHHIMPS: A Mnemonic for the Life-threatening Causes of Delirium

Withdrawal
Wernicke encephalopathy
Hypoxia or hypoperfusion of the brain
Hypertensive crisis
Hypoglycemia
Hyper- or hypothermia
Intracranial mass or hemorrhage
Meningitis or encephalitis
Poisons (including medications)
Status epilepticus

Adapted from Wise MG, Trzepacz PT. Delirium (confusional states). In: Rundell JR, Wise MD, eds. *The American psychiatric press textbook of consultation-liaison psychiatry*. Washington, DC: American Psychiatric Press, 1996:258–274.

III. DIFFERENTIAL DIAGNOSIS

A. Two delirium screening scales have been validated for use by nonpsychiatric personnel in the ICU: the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Both are available at www.icudelirium.org.

B. Delirious patients may present with a hypoactive subtype that is commonly mistaken for *depression*. Hypoactive delirium is distressing to the patient, may progress to the agitated form, and requires appropriate treatment.

C. Patients with *dementia* are at risk for agitation and delirium in the ICU as a result of being in unfamiliar surroundings. Behavioral measures should be employed to help these patients maintain orientation to their milieu.

D. Patients with *schizophrenia* also may have difficulty adapting to ICU restrictions. Measures should be taken to make the ICU as familiar and comfortable as possible. Table 142-2 compares and contrasts the diagnostic features of these different causes of agitation.

TABLE 142-2 Differential Diagnosis of Causes of Agitation

	Delirium	Dementia	Depression	Schizophrenia
Onset	Acute	Insidious[a]	Variable	Variable
Course	Fluctuating	Progressive[b]	Variable	Variable
Reversibility	Usually	Not usually	Usually	No
Level of consciousness	Impaired	Clear until late stages	Unimpaired	Unimpaired[c]
Attention/ memory	Inattention, poor memory	Poor memory without marked inattention	Attention usually intact, memory intact	Poor attention, memory intact
Hallucinations	Usually visual; can be auditory, tactile, gustatory, olfactory	Can be visual or auditory	Usually auditory	Usually auditory
Delusions	Fleeting, fragmented, usually persecutory	Paranoid, often fixed	Complex, mood-congruent	Frequent, complex, systematized, often paranoid

[a]Except for dementia due to stroke.
[b]Lewy body dementia often presents with a waxing and waning course imposed on an overall progressive decline.
[c]Except when complicated by catatonia.
Adapted from Trzepacz PT, Meagher DJ. Delirium. In: Levenson JL, ed. *The American Psychiatric Publishing textbook of psychosomatic medicine*. Washington, DC: American Psychiatric Publishing, 2005:91–130.

E. *Alcohol or sedative-hypnotic withdrawal* is a prominent cause of delirium in the ICU. This syndrome results from decreased activity of γ-aminobutyric acid (GABA) and unopposed noradrenergic, glutamatergic, and dopaminergic activation when the intake of alcohol or sedative-hypnotic agents is ceased suddenly. Confusion, agitation, diaphoresis, tremor, and autonomic instability (collectively known as delirium tremens) may progress to seizure and death.

F. Inadequately controlled pain, overwhelming anxiety, or hopelessness resulting from depression also may result in agitation.

IV. TREATMENT

A. Definitive treatment of delirium requires identification and treatment of the underlying causes.

B. Agitation and other symptoms of delirium may be managed adjunctively with neuroleptics due to their antagonism of the dopamine receptor.

C. The "gold standard" of this adjunctive treatment is intravenous (IV) haloperidol. IV administration, although "off label," is the standard of care and is preferable to other routes due to better absorption, less discomfort, and reduced extrapyramidal side effects (EPS).

1. Treatment with IV haloperidol is usually initiated with a dose ranging from 0.5 mg (in the elderly) to 10 mg (for severe agitation). Subsequent doses can be doubled at 30-minute intervals until optimal tranquilization is achieved.
2. Complete absence of agitation should be the goal, after which a fraction of the cumulative dose of haloperidol required to control the agitation can be divided and given 2 or 3 times daily with additional doses provided as needed.
3. Over time, the total dose can be gradually decreased; it is usually wise to wean the evening dose last.

D. Data on the efficacy and safety of the atypical or second-generation neuroleptic agents (e.g., risperidone, olanzapine, quetiapine, ziprasidone) in the delirious patient are limited, though single randomized, controlled trials have found both risperidone and olanzapine to be as effective as haloperidol.

E. Quetiapine may have a niche role in the treatment of delirium in patients with Parkinson disease or Lewy body dementia, as it is less likely than haloperidol to exacerbate these disorders.

F. Treatment of alcohol or sedative-hypnotic withdrawal typically requires administration of a benzodiazepine (e.g., lorazepam). Great care should be taken in the diagnosis of alcohol or sedative-hypnotic withdrawal in the agitated patient, since the prescribed treatment (i.e., a benzodiazepine) is almost certain to exacerbate delirium due to another etiology.

V. COMPLICATIONS

A. Delirium has been associated with prolonged hospital stay and increased morbidity and mortality. Fiscally, delirium predicts heightened costs in the ICU and in overall hospital care.

B. Neuroleptic administration may contribute to progressive widening of the QT interval, resulting in an increased risk for torsades de pointes (TDP) and possible death.

1. Although the incidence of fatal TDP is relatively low, cardiac rhythm should be carefully monitored with close attention paid to serum levels of potassium, magnesium, and calcium.
2. Prolongation of the corrected QT interval (QTc) >25% from baseline or a QTc >500 ms may warrant telemetry, cardiologic consultation, and reduction or discontinuation of haloperidol.
3. Other potential QTc-prolonging agents (e.g., fluoroquinolone antibiotics, calcium channel blockers, methadone) may need to be discontinued.

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143 Suicide

Saori A. Murakami

I. GENERAL PRINCIPLES

A. Description.

1. The treatment of a suicidal patient in the intensive care unit (ICU) includes evaluation, management, and safeguarding the patient.
2. Evaluation and management of the suicidal patient require an understanding of risk factors, protective factors, the interplay among these elements, and the relationship between the staff and the patient.
3. Psychiatric care is essential during and after the stabilization of medical problems. It is helpful to initiate psychiatric involvement from the beginning of the admission, even if the patient is intubated and heavily sedated. In these circumstances, the consulting psychiatrist can obtain collateral information, assess the severity and lethality of the attempt, establish the chronology of symptoms leading to the presentation, and conduct serial safety assessments.

B. Risk and protective factors.

1. Suicide is the 10th leading cause of death in the United States (as of 2009, 7th in men, 14th in women).
2. It is not possible to make absolute predictions of suicidal behavior.
3. Risk factors for suicide include sociodemographic factors, past and current psychiatric and medical illnesses, family history, and psychosocial stressors (Table 143-1).
4. Protective factors include the absence of these risk factors and the presence of support from medical treaters, family, and community.
5. Assessment of risk and protective factors must be conducted on a case-by-case basis.

II. TREATMENT

A. Nonpharmacologic interventions.

1. Suicidal thinking can be expressed in various ways, including explicit declaration or implicit action (e.g., refusal to eat or to cooperate with care). All forms of suicidal thinking require immediate attention.
2. Monitoring is essential and can be accomplished through 1:1 observation or frequent checking on the patient. In some situations, physical restraints may be necessary.
3. The ICU staff should be aware of potential means by which the patient may harm himself or herself, including personal belongings and items brought in by visitors.

TABLE 143-1 Risk Factors for Suicide

Sociodemographic factors
- Age: late adolescence to young adulthood, older than 65 y
- Gender: men are more likely to complete suicide, women more likely to attempt
- Race: non-Hispanic white, Native American, Alaskan native
- Marital status: divorced or widowed > single > married
- Access to lethal agents

Psychiatric history and present psychiatric illness
- Psychiatric disorders
- Substance abuse
- History of suicide attempts
- Hopelessness or negative expectations about the future
- Recent discharge from a psychiatric hospital

Medical history and present medical illness
- Neurologic disorders
- Head trauma
- Cognitive deficits
- Malignancies
- Human immunodeficiency virus infection
- Chronic pain syndromes
- Chronic inflammatory disease
- Chronic renal failure
- Heart disease
- Chronic pulmonary disease

Family history
- Psychiatric illness or substance abuse
- History of completed suicide

Psychosocial stressors
- Family life
- Work life
- Relationships
- Finances
- Recent real or perceived loss
- Few supports
- Tumultuous early family environment

Adapted from Brendel R, Wei M, Lagomasino IT, et al. Care of the suicidal patient. In: Stern TA, Fricchione GL, Cassem NH, et al., eds. *Massachusetts general hospital handbook of general hospital psychiatry,* 6th ed. Philadelphia: Saunders, 2010:541–554.

4. Safety assessments should be made at least daily.
5. The primary team should identify and address negative feelings that may be induced by some suicidal patients, particularly those who have made multiple attempts or who clamor for the attention of the ICU staff.

B. Medications.

1. Consideration should be given to discontinuing or decreasing the dose of medications that may heighten impulsivity or disinhibition (e.g., benzodiazepines and anticholinergic agents).
2. Establishing an accurate psychiatric diagnosis will guide the decision to start or restart psychiatric medications following a suicide attempt. Outpatient medications should not be resumed reflexively.
   a. The patient's physical condition, sensorium, and risk for seizures and arrhythmias, as well as medication side effects, should be considered.
3. While treating the underlying psychiatric diagnosis with medications will assist in lowering overall suicide risk, psychotropic medications have not independently been associated with a decrease in suicide.

C. Psychiatric consultation.

1. Psychiatric consultation is strongly recommended whenever there is a question regarding the potential for self-harm.
   a. This is particularly important in cases of implicit action or when there are overwhelming risk factors even without an explicit declaration.
2. The primary team should provide the consultant with as many details of the suicide attempt as possible. When an explicit declaration has been made, the team should inform the consultant of the exact words used and the context of the statement.
3. Clear documentation is important.
4. Consultation can also be helpful in understanding and processing the psychological dynamics between the patient and staff.

D. Disposition.

1. The most common options for discharge are home or a psychiatric facility.
2. This decision is usually made with the help of the psychiatric consultant, who will assist with placement, insurance authorization, and legal matters (e.g., involuntary commitment if the patient is unwilling to be hospitalized psychiatrically).

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144 Diagnosis and Treatment of Depression in the Intensive Care Unit Patient

John Querques and Theodore A. Stern

I. GENERAL PRINCIPLES

A. Major depressive disorder is a psychiatric condition that affects mood and neurovegetative functions (e.g., sleep, appetite).

1. While experiencing a depressed mood transiently can be a normal and expected part of life, having the full constellation of symptoms meeting the criteria for major depressive disorder is never a normal or appropriate reaction to a stressful situation.
2. Left untreated, major depression increases rates of morbidity and mortality, especially from cardiac conditions.

B. Definition.

1. Major depressive disorder is a syndrome characterized by five or more of the symptoms listed in Table 144-1 for 2 weeks or more.
2. One of the five symptoms must be either depressed mood or anhedonia (i.e., an absence of pleasure).
3. The mnemonic SIG: E CAPS (i.e., label: energy capsules) is a helpful guide to remember these defining criteria (Table 144-1).

II. DIAGNOSIS

A. Clinical features. The manifestations of depression include affective, behavioral, and cognitive abnormalities (i.e., the ABCs of depression) (Table 144-2). Though a depressed patient may be psychomotorically slowed and have scant facial expression, his or her sensorium will be intact. This helps to distinguish depression from delirium, in which the patient will have a reduced level of wakefulness, alertness, and/or attentiveness. The hypomanic or manic patient will have an elevated, expansive, or irritable mood rather than a dysphoric one.

B. Differential diagnosis. Depression in the intensive care unit (ICU) can occur as a primary affective disorder (e.g., major depressive disorder), a mood disorder associated with a specific medical condition or its treatment, or a psychological reaction to an acute medical illness.

TABLE 144-1 Mnemonic for the Diagnostic Criteria for a Depressive Episode—SIG: E CAPS

Depressed mood
Sleep (increased or decreased)
Interest (decreased)
Guilt (preoccupation with feeling guilty or worthless)
Energy (decreased)
Concentration (decreased)
Appetite disturbed (increased or decreased) or weight gain or loss
Psychomotor agitation or retardation
Suicidal thinking or thoughts of death

Adapted from American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association, 1994.

TABLE 144-2 Affective, Behavioral, and Cognitive Features of Depression—the ABCs

Affective symptoms
- Depressed mood
- Hopelessness
- Crying
- Irritability
- Anger
- Decreased interest

Behavioral symptoms
- Insomnia
- Anorexia
- Apathy
- Increased sleep
- Increased appetite
- Decreased energy
- Psychomotor agitation
- Psychomotor retardation
- Noncompliance
- Deliberate self-harm
- Impulsivity
- Poor eye contact
- Increased or intractable pain

Cognitive symptoms
- Guilty rumination
- Decreased concentration
- Suicidal thinking or thoughts of death
- Confusion
- Dementia-like symptoms
- Somatic preoccupation

Adapted from Geringer ES, Querques J, Kolodziej MS, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012:2087–2099.

TABLE 144-3 Selected Medical Conditions Associated with Depression

Cardiovascular
- Congestive heart failure
- Hypertensive encephalopathy

Collagen vascular
- Systemic lupus erythematosus

Endocrine
- Diabetes mellitus
- Hypo- and hyperadrenalism
- Hypo- and hyperparathyroidism
- Hypo- and hyperthyroidism

Infectious
- Hepatitis
- Human immunodeficiency virus infection
- Mononucleosis

Metabolic
- Acid–base disorders
- Hypokalemia
- Hypo- and hypernatremia
- Renal failure

Neoplastic
- Carcinoid syndrome
- Pancreatic carcinoma
- Paraneoplastic syndromes

Neurologic
- Brain tumor
- Multiple sclerosis
- Parkinson disease
- Complex partial seizures
- Stroke
- Subcortical dementia

Nutritional
- Vitamin B_{12} deficiency (pernicious anemia)
- Thiamine deficiency (Wernicke encephalopathy)

Adapted from Geringer ES, Querques J, Kolodziej MS, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012:2087–2099.

1. Medical causes. Various medical conditions (Table 144-3) and medications (Table 144-4) can cause depression. Laboratory testing should be guided by results of a comprehensive history and physical examination.
2. Psychological reaction. Critical illness often threatens a patient's sense of physical integrity, autonomy, and control and can remind a patient of either a personal or family history of similar life-threatening circumstances.

TABLE 144-4 Selected Medications Associated with Depression

Acyclovir (especially at high doses)
Anticonvulsants (at high doses or plasma levels): carbamazepine, phenytoin, primidone
Antihypertensives: thiazides, clonidine, nifedipine, prazosin
Baclofen
Barbiturates
Benzodiazepines
β-Blockers
Bromocriptine
Contraceptives
Corticosteroids
Cycloserine
Dapsone
Digitalis (at high doses or in elderly patients)
Diltiazem
Disopyramide
Halothane (postoperatively)
Histamine-2 receptor antagonists
Interferon-α
Isoniazid
Levodopa (especially in elderly patients)
Mefloquine
Metoclopramide
Narcotics
Nonsteroidal anti-inflammatory drugs
Phenylephrine
Phenylpropanolamine (withdrawal)
Procaine derivatives: penicillin G procaine, lidocaine, procainamide
Thyroid hormone
Trimethoprim-sulfamethoxazole

Adapted from Geringer ES, Querques J, Kolodziej MS, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2012:2087–2099.

III. TREATMENT

A. Management of depression includes pharmacologic treatment, psychological interventions, and/or electroconvulsive therapy (ECT).

B. Pharmacologic treatment. In the ICU, medications are used most frequently (Table 144-5). An antidepressant medication is selected based on its side effect profile and its rapidity of action.

1. Psychostimulants.

a. Dextroamphetamine and methylphenidate work within hours to days.

b. Stimulants can cause or contribute to tachycardia, hypertension, arrhythmias, and coronary spasm, but rarely do so at the low doses (5 to 20 mg daily) usually used.

TABLE 144-5 Usual Starting Doses of Antidepressant Agents in Critically Ill Patients

Agent	Usual starting dose (mg/day)
SSRIs	
Citalopram	5–10
Escitalopram	5–10
Fluoxetine	5–10
Paroxetine	5–10
Sertraline	25–50
SNRIs	
Duloxetine	30–60
Venlafaxine	37.5–75
Others	
Bupropion	50–100
Dextroamphetamine	2.5–5
Methylphenidate	5
Mirtazapine	7.5–15

c. Bupropion and modafinil also can be used for their stimulant-like effects; they usually have some effect within a few days to a week, certainly earlier than the selective serotonin reuptake inhibitors (SSRIs).

2. Selective serotonin reuptake inhibitors.
- **a.** SSRIs exert their therapeutic effect within 4 weeks.
- **b.** SSRIs can cause agitation, irritability, insomnia, tremulousness, diaphoresis, anorexia, nausea, vomiting, diarrhea, and sexual dysfunction.
- **c.** SSRIs, when given in combination with other serotonergic drugs (rarely when used alone), can cause serotonin syndrome, an uncommon but potentially fatal condition of serotonergic hyperstimulation characterized by confusion, agitation, incoordination, tremor, myoclonus, diaphoresis, shivering, diarrhea, hyperthermia, and hyperreflexia. Treatment of serotonin syndrome is largely supportive and includes discontinuation of the offending agents.
- **d.** SSRIs have fewer cardiovascular effects than tricyclic antidepressants (TCAs) and do not commonly cause orthostatic hypotension.
- **e.** SSRIs are extensively metabolized by the hepatic cytochrome P (CYP)-450 system.
- **f.** All SSRIs, except citalopram and escitalopram, inhibit the CYP-450 pathway and raise serum levels of coadministered drugs (Table 144-5).

3. Serotonin–norepinephrine reuptake inhibitors (SNRIs).
- **a.** Venlafaxine.
  - **i.** Venlafaxine exerts its therapeutic effect within 4 weeks, a timeframe similar to that of SSRIs.

ii. Venlafaxine can cause a dose-dependent increase in supine diastolic blood pressure.
iii. Venlafaxine does not inhibit the CYP-450 system.

b. Duloxetine.
i. Duloxetine exerts its therapeutic effect within 4 weeks, similar to the time course of SSRIs.
ii. Duloxetine is also U.S. Food and Drug Administration (FDA) approved for the treatment of diabetic neuropathy.

4. α_2-Adrenergic receptor antagonist.
a. Mirtazapine.
i. Mirtazapine enhances presynaptic release of norepinephrine and serotonin.
ii. Mirtazapine improves sleep and appetite within a few days, while a full antidepressant effect usually develops within 4 weeks.
iii. Mirtazapine is available in an orally disintegrating formulation that is useful in patients who cannot swallow pills.

5. TCAs.
a. TCAs exert their therapeutic effect within 4 weeks.
b. TCAs can cause sedation, confusion, blurred vision, dry mouth, constipation, orthostatic hypotension, and disturbances of cardiac conduction and rhythm.
c. TCAs should be used with great caution in patients.
i. With preexisting conduction delays.
ii. With a corrected QT interval (QTc) of >440 ms.
iii. Who are taking other drugs that also have type I antiarrhythmic effects.

6. Monoamine oxidase inhibitors (MAOIs).
a. MAOIs exert their therapeutic effect within 4 weeks.
b. Phenelzine and tranylcypromine are not recommended in the ICU because of the profound hypertensive crises that might result when these agents are combined with pressors.

C. Psychological. Patients often benefit from information, clarification, reassurance, and support. Asking about a patient's family, work, hobbies, and interests helps to restore his or her sense of identity.

D. ECT. ECT is reserved for patients with severe or delusional depression and for those who cannot tolerate, or have failed to respond to, pharmacologic and psychological therapies.

SUGGESTED READINGS

Cassano P, Cassem NH, Papakostas GI, et al. Mood-disordered patients. In: Stern TA, Fricchione GL, Cassem NH, et al., eds. *Massachusetts general hospital handbook of general hospital psychiatry*, 6th ed. Philadelphia: Saunders Elsevier, 2010:73–92.
A comprehensive review of the characteristics of depressive disorders, their differential diagnosis, and their treatment in the context of comorbid medical illness.

Fava M, Papakostas GI. Antidepressants. In: Stern TA, Rosenbaum JF, Fava M, et al., eds. *Massachusetts general hospital comprehensive clinical psychiatry*. Philadelphia: Mosby Elsevier, 2008:595–619.
A comprehensive review of the entire antidepressant armamentarium.

Appendix

Calculations Commonly Used in Critical Care

Joseph J. Frassica

A. FAHRENHEIT AND CELSIUS TEMPERATURE CONVERSIONS

°C	°F	°C	°F
45	113.0	34	93.2
44	111.2	33	91.4
43	109.4	32	89.6
42	107.6	31	87.8
41	105.8	30	86
40	104.0	29	84.2
39	102.2	28	82.4
38	100.4	27	80.6
37	98.6	26	78.8
36.8	98.2	25	77
36	96.8	24	75.2
35	95		

°C to °F: °F = (°C × 9/5) + 32
°F to °C: °C = (°F − 32) × 5/9

B. ACTIONS OF COMMON INTRAVENOUS VASOACTIVE DRUGS

	α	β_1	β_2
Dopamine	+	+	0[a]
	++	+++	0[b]
	+++	++	0[c]
Dobutamine	+	+++	++
Norepinephrine	+++	++	+
Epinephrine	++	+++	+++
Isoproterenol	0	+++	+++
Phenylephrine	+++	0	0
Vasopressin	0	0	0

[a]Low 1–2 μg/kg/min.
[b]Mid 2–10 μg/kg/min.
[c]High >10 μg/kg/min.

C. HEMODYNAMIC CALCULATIONS

MEAN ARTERIAL BLOOD PRESSURE (mm Hg)
= MAP
= [systolic BP + (2 × diastolic BP)]/3
= diastolic BP + 1/3 (systolic BP − diastolic BP)
Normal range: 85 to 95 mm Hg

FICK EQUATION FOR CARDIAC INDEX (L/min/m^2)
= CI
= CO/BSA
= oxygen consumption/(arterial O_2 content − venous O_2 content)
= [10 × $\dot{V}O_2$ (mL/min/m^2)]/[Hgb (g/dL) × 1.39 × (arterial % saturation − venous % saturation)].
Normal range: 2.5 to 4.2 L/min/m^2

SYSTEMIC VASCULAR RESISTANCE (dyne/sec/cm^5)
= SVR
= [80 × (MAP − right atrial mean BP)]/CO (L/min)
Normal range: 770 to 1,500 dyne/sec/cm^5

PULMONARY VASCULAR RESISTANCE (dyne/sec/cm^5)
= PVR
= [80 × (pulmonary artery mean BP − pulmonary capillary wedge pressure)]/CO (L/min)
Normal range: 20 to 120 dyne/sec/cm^5

D. PULMONARY CALCULATIONS

ALVEOLAR GAS EQUATION (mm Hg)
$P_Ao_2 = PIO_2 - (Paco_2/R)$
$= [FIO_2 \times (P_{atm} - P_{H2O})] - (Paco_2/R)$
$= 150 - (Paco_2/R)$ (on room air, at sea level)
Normal value: ~100 mm Hg (on room air, at sea level)

ALVEOLAR–ARTERIAL OXYGEN TENSION GRADIENT (mm Hg)
= A − a gradient
$= PAo_2 - Pao_2$
Normal values (upright): 2.5 + (0.21 × age)

ARTERIAL BLOOD OXYGEN CONTENT (mL/dL)
$= Cao_2$
= oxygen dissolved in blood + oxygen carried by hemoglobin
$= [0.0031 (mL\ o_2/dL) \times Pao_2] + [1.39 \times Hgb\ (g/dL) \times \%\ Hgb\ saturated\ with\ O_2]$
Normal range: 17.5 to 23.5 mL/dL

COMPLIANCE (mL/cm H_2O) = ΔVolume/ΔPressure
On Mechanical Ventilation:
Static respiratory system compliance = C_{st} = Tidal volume/($P_{plateau} - P_{end\ exp}$)
Dynamic effective compliance = C_{dyn} = Tidal volume/($P_{peak} - P_{end\ exp}$)

E. ELECTROLYTE AND RENAL CALCULATIONS

ANION GAP (mEq/L)
$= [Na^+] - ([Cl^-] + [HCO_3^-])$
Normal range: 9 to 13 mEq/L

EXPECTED ANION GAP IN HYPOALBUMINEMIA
$= 3 \times$ [albumin (g/dL)]

CALCULATED SERUM OSMOLALITY (mOsm/kg)
$= (2 \times [Na^+]) + ([glucose]/18) + ([BUN]/2.8)$
Normal range: 275 to 290 mOsm/kg

OSMOLAR GAP (mOsm/kg)
= Measured serum osmolality − Calculated serum osmolality
Normal range: 0 to 5 mOsm/kg

Na^+ CORRECTION FOR HYPERGLYCEMIA
Increase $[Na^+]$ by 1.6 mEq/L for each 100 mg/dL increase in [glucose] above 100 mg/dL

Ca^{2+} CORRECTION FOR HYPOALBUMINEMIA
Increase $[Ca^{2+}]$ by 0.8 mg/dL for each 1.0 g/dL decrease in [albumin] from 4 g/dL

WATER DEFICIT IN HYPERNATREMIA (L)
$= [0.6 \times$ body weight (kg)$] \times \{([Na^+]/140) - 1\}$

Na^+ DEFICIT IN HYPONATREMIA (mEq)
$= [0.6 \times$ body weight (kg)$] \times$ (desired plasma $[Na^+] - 140$)

FRACTIONAL EXCRETION OF SODIUM (%)
$= F_ENa$
$= \{$(excreted $[Na^+]$)/(filtered $[Na^+]$)$\} \times 100$
$= \{$(urine $[Na^+]$)/(serum $[Na^+]$)$\}/\{$(urine [Creat])/(serum [Creat])$\} \times 100$

CREATININE CLEARANCE (mL/min)
= (urine [Creat]) × (urine volume over 24 h)
= {(urine [Creat (g/dL)])
× {[urine volume (mL/d)]/1,440 (min/day)]}/serum [Creat] (mg/dL)
Estimated for males
$= \{(140 -$ age$) \times$ [lean body weight (kg)]$\}/\{$serum [Creat] (mg/dL) $\times 72\}$
Estimated for females = 0.85 × (estimate for males)
Normal range: 74 to 160 mL/min

F. ACID–BASE FORMULAS

HENDERSON EQUATION FOR $[H^+]$
$[H^+]$ (nm/L) $= 24 \times \{Paco_2/[HCO_3^-]\}$
Normal values: $[H^+]$ is 40 nm/L at pH of 7.40 and each 0.01 unit change in pH corresponds to an approximate opposite deviation of $[H^+]$ of 1 nm/L (over the pH range of 7.10 to 7.50)

METABOLIC ACIDOSIS
Bicarbonate deficit (mEq/L) $= (0.4 + [2.6/HCO_3^-])$
$\times$ lean body weight (kg) $\times (24 - [HCO_3^-])$

Expected $Paco_2$ compensation = $(1.5 \times [HCO_3^-]) + 8 \pm 2$

RESPIRATORY ACIDOSIS
Acute = $\Delta[H^+]/\Delta Paco_2 = 0.8$
Chronic = $\Delta[H^+]/\Delta Paco_2 = 0.3$

RESPIRATORY ALKALOSIS
Acute = $\Delta[H^+]/\Delta Paco_2 = 0.8$
Chronic = $\Delta[H^+]/\Delta Paco_2 = 0.17$

G. NEUROLOGIC CALCULATIONS

GLASGOW COMA SCALE
= eye score (1–4) + motor score (1–6) + verbal score (1–5)

Specific Components of the Glasgow Coma Scale:

Component	Score
Eye opening	
Spontaneous	4
To speech	3
To painful stimuli	2
Eye opening not observed	1
Motor response	
Obeys commands	6
Localizes	5
Withdrawal response	4
Abnormal flexion response	3
Abnormal extension response	2
No motor response	1
Verbal response	
Oriented	5
Confused/conversant	4
Uses inappropriate words	3
Incomprehensible	2
No verbal response	1
Normal total value: 15 (range 3–15)	

H. PHARMACOLOGIC CALCULATIONS

DRUG ELIMINATION CONSTANT
= Ke
= fractional elimination of drug per unit time
= $\{\ln([peak]/[trough])/(t_{peak} - t_{trough})\}$

DRUG HALF-LIFE
= $t^{1/2}$
= 0.693/Ke

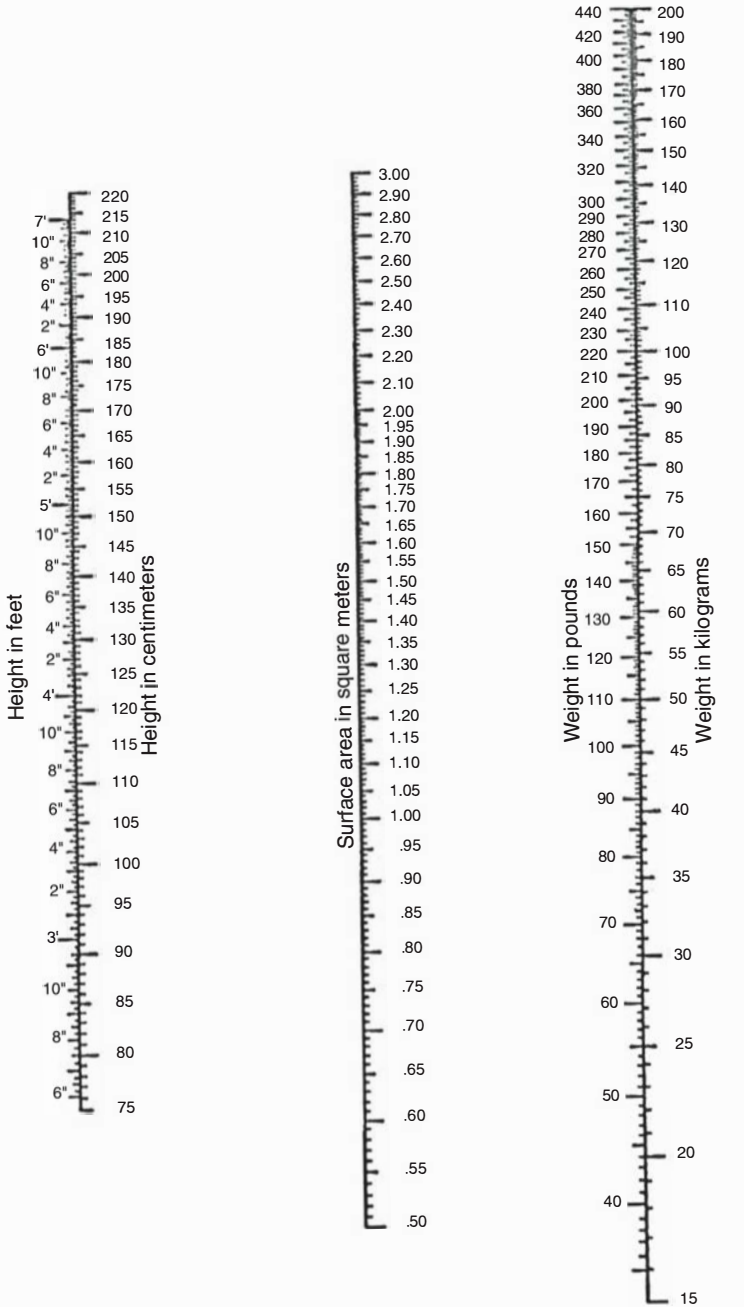
Height in feet
7'
10"
8"
6"
4"
2"
6'
10"
8"
6"
4"
2"
5'
10"
8"
6"
4"
2"
4'
10"
8"
6"
4"
2"
3'
10"
8"
6"
Height in centimeters
220
215
210
205
200
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
Surface area in square meters
3.00
2.90
2.80
2.70
2.60
2.50
2.40
2.30
2.20
2.10
2.00
1.95
1.90
1.85
1.80
1.75
1.70
1.65
1.60
1.55
1.50
1.45
1.40
1.35
1.30
1.25
1.20
1.15
1.10
1.05
1.00
.95
.90
.85
.80
.75
.70
.65
.60
.55
.50
Weight in pounds
440
420
400
380
360
340
320
300
290
280
270
260
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
Weight in kilograms
200
190
180
170
160
150
140
130
120
110
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15

Figure A-1.

VOLUME OF DISTRIBUTION (L/kg)
= Vd
= [(dose) × (fraction of active drug in circulation)]/[(area under single dose curve) × Ke]

DRUG CLEARANCE
= Vd × Ke

DRUG LOADING DOSE
= Vd × [target peak]

DRUG DOSING INTERVAL
= {$-Ke^{-1}$ × ln ([desired trough]/[desired peak])} + infusion time (h)

I. NUTRITIONAL CALCULATIONS

BODY MASS INDEX
= BMI
= weight (kg)/[height (cm)]^2

RESPIRATORY QUOTIENT
= R
= CO_2 production (mL/min)/O_2 consumption (mL/min)
Normal value: 0.8

HARRIS-BENEDICT EQUATION OF RESTING ENERGY EXPENDITURE (kcal/day)
Males = 66 + [13.7 × weight (kg)] + [5 × height (cm)] − (6.8 × age)
Females = 655 + [9.6 × weight (kg)] + [1.8 × height (cm)] − (4.7 × age)

J. BODY SURFACE AREA FORMULA AND NOMOGRAM (ADULT)

BODY SURFACE AREA
= BSA
= (height [cm])$^{0.718}$ × (weight [kg])$^{0.427}$ × 74.49
To use the adult nomogram (Fig. A-1), place a straightedge connecting the persons' weight in the right column with their height in the left column. The point where the straightedge crosses the center column denotes that persons' body surface area in square meters.

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Note: Page numbers followed by f *indicate a figure;* t *following a page number indicates tabular material*

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